FORM PTO-1390 (REV 10-2000) | U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	US APPLICATION NO (If known, see 37 CFR 1 5)
661-50303	09/700906

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/03451	20 May 1999	22 May 1998

TITLE OF INVENTION: ANTISENSE OLIGONUCLEOTIDES FOR TREATING PROLIFERATING CELLS

APPLICANT(S) FOR DO/EO/US: Flad, Hans-Dieter; Bohle, Andreas; Deinert, Irina

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U S C 371.
3. [ ] This is an express request to promptly begin national examination procedures (35 U S.C 371(f)).
4. [X] The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [X] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: Amend claims 4-8, 10 and 13 as follows, prior to calculating claim fees and without prejudice:

Claim 4, line 1, delete "bis 3".
Claim 5, line 1, delete "bis 4".
Claim 6, line 1, delete "bis 5".
Claim 7, line 1, delete "bis 6".
Claim 8, line 1, delete "bis 7".
Claim 10, line 1, delete "bis 8".
Claim 13, line 1, delete "oder 12".

The Claims have been amended to remove multiple dependency only. No claims have been amended to overcome prior art.

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	526 Rec'd PCT/PTO 21 NOV 2000	ATTORNEY'S DOCKET NUMBER
09/700906	PCT/EP99/03451		661-50303

17. ☒ The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	15 - 20 =	0	X **$18.00**	$
Independent claims	3 - 3 =	0	X **$80.00**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$

TOTAL OF ABOVE CALCULATIONS =	$ 990
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.	$
SUBTOTAL =	$ 990
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +	$ 130
TOTAL NATIONAL FEE =	$ 1,120
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +	$
TOTAL FEES ENCLOSED =	$1,120
Amount to be refunded:	$
charged:	$ 1,120

a. ☒ A check in the amount of $1,120 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-0687. A duplicate copy of this sheet is enclosed.

Under Order No.: 62-661

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Customer No. 20736

SIGNATURE

Jeffrey S. Melcher

NAME

35,950

REGISTRATION NUMBER

November 21, 2000

526 Rec'd PCT/PTO 21 NOV 2000

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/700906	PCT/EP99/03451	661-50303

17. [x] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [x] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	15	- 20 =	0	X **$18.00**	$
Independent claims	3	- 3 =	0	X **$80.00**	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ **$270.00**	$

TOTAL OF ABOVE CALCULATIONS =	$ 990
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.	$
SUBTOTAL =	$ 990
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [x] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +	$ 130
TOTAL NATIONAL FEE =	$ 1,120
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +	$
TOTAL FEES ENCLOSED =	$1,120
Amount to be refunded:	$
charged:	$ 1,120

a. [x] A check in the amount of $1,120 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

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Under Order No.: 62-661

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Customer No. 20736

COPY

SIGNATURE

Jeffrey S. Melcher

NAME

35,950

REGISTRATION NUMBER

PTO RECEIPT FOR INDICATED ITEMS

Transmittal Letter to US Designated Office Concerning Filing Under 35 USC 371
International Application No.: PCT/EP99/03451
Inventor: Flad
Title: Antisense Oligonucleotides for Treating Proliferating Cells
Attorney Docket No.: 661-50303
Preliminary Amendment
Fee Sheet

Check for $1,120.

The PTO did not receive the following listed item(s)
~~No Preliminary Amendment~~
~~09/700906~~

Current Due Date: November 22, 2000

527 Rec'd PCT/PTO 21 NOV 2000

Certification of Translation

I, Heinz-Peter Muth of UEXKÜLL & STOLBERG, Patent Attorneys in Hamburg, Germany, do hereby certify that I am conversant with the English and German languages and am a competent translator thereof, and I further certify that to the best of my knowledge and belief the foregoing is a true and correct translation made by me of the International Application No. PCT/EP99/03451 filed May 20, 1999 into the English language.

Hamburg, January 5, 2001

Heinz-Peter Muth

Antisense oligonucleotides for treatment of proliferating cells

The invention relates to oligoribo- and oligodeoxyribonucleotides which are suitable for treating pathological conditions accompanied by an increased cell proliferation.

Nucleic acid fragments of which the sequence is complementary to the coding or "sense" strand of DNA or a messenger RNA (mRNA) and which are therefore capable of binding specifically to these complementary target sequences (hybridizing) are called antisense oligonucleotides. Selective influencing of cell processes is possible by this means. Antisense oligonucleotides have found interest as tools in research and as potential agents for antiviral and tumour therapy (E. Uhlmann, A. Peyman, Chemical Reviews, **90** (1990) 544-584; S. Agrawal, TIBTECH **10** (1992) 152-158) and in some cases have already reached the stage of clinical research (M.D. Matteucci, R.W. Wagner, Nature **384** (196) 20-22).

Ki-67 is a cell protein which is produced in all active phases of the cell cycle (G_1, S, G_2 and mitosis), but not during the resting phase (G_0). The resting or G_0 phase describes the state in which the dividing activity of the cell is at rest, i.e. the cells have left the active phases of the cell cycle and do not divide. Ki-67 is a human nuclear protein, expression of which is associated strictly with cell proliferation. Specific antibodies against the Ki-67 protein are used in histopathology for determination of the proportion of growing cells in human tumours (J. Gerdes, Seminars in Cancer Biology 1 (1990) 199-206).

It has furthermore been found that proliferation of human IM-9 cells can be inhibited as a function of the concentration by a Ki-67 protein antisense 2'-deoxyoligonucleotide comprising 21

bases (C. Schlüter et al., The Journal of Cell Biology, **123** (1993) 513-522). The complete nucleotide sequence of the cDNA of the Ki-67 protein and the derived amino acid sequence are known (Schlüter et al., loc. cit.). Figure 1 (SEQ ID NO 1) shows the sense strand of the Ki-67 cDNA.

The object of the present invention is to provide antisense oligonucleotides which are suitable for treating pathological conditions accompanied by an increased cell proliferation. Examples of such disease states are tumours, allergies, autoimmune diseases, cicatrization, inflammations and rheumatic diseases, as well as suppression of rejection reactions in case of transplantations.

This object has been achieved by oligoribo- or oligodeoxyribonucleotides, and physiologically acceptable salts thereof, which are capable of hybridizing with the mRNA which codes for the protein Ki-67.

It has been found that the oligoribo- or oligodeoxyribonucleotides according to the invention have a cytotoxic and not only inhibiting action on proliferating cells, such as, for example, tumour cells, and cause the death of the cells. This finding is surprising in as much as the Ki-67 protein is not detectable in non-proliferating cells and is thus evidently not necessary for survival of the cells.

Oligonucleotides which hybridise with Ki-67 mRNA at 37ºC and a physiological saline concentration are preferred.

Oligoribo- and oligodeoxyribonucleotides, and in particular oligodeoxyribonucleotides, of which the sequence is complementary to the nucleotide sequence, shown in figure 1 (SEQ ID NO: 1), of the sense strand of the cDNA of Ki-67, i.e. at a chain length of 10 bases has not more than 0 to 4, preferably 0 to 2, and even more preferably no mismatches, are particularly preferred.

Oligoribo- and oligodeoxyribonucleotides which hybridise with a nucleotide sequence from the 5' region of the Ki-67 mRNA, i.e. oligoribo- or oligodeoxyribonucleotides which are complementary to the 5' region of the sequence shown in figure 1, preferably to a section of the region from position 197 to 2673 or 2673 to 9962, particularly preferably 197 to 220, have furthermore proved to be particularly active.

The oligonucleotides according to the invention preferably have a chain length of 12 to 66 nucleotides, particularly preferably 17 to 46 and very particularly preferably 22 to 46 nucleotides.

The sequence (SEQ ID NO: 3):

(5'-ACC AGG CGT CTC GTG GGC CAC AT)

is very particularly preferred.

Non-modified oligonucleotides, and in particular non-modified oligoribonucleotides, are subject to nucleolytic degradation to a high degree and therefore have only a low stability and biological half-life. To improve ability to penetrate through membranes and to increase the biological half-life, the bases, sugar residues and/or phosphate residues of the oligonucleotides according to the invention are preferably modified.

Oligonucleotides in which one or more phosphate groups are replaced by phosphothioate, methylphosphonate, phosphoramidate, methylene(methylimino) (MMI) and/or guanidine groups are preferred. The structure of these groups is shown in figure 2. Thiolated oligonucleotides, i.e. oligonucleotides in which phosphate groups are replaced by phosphothioate groups, are particularly preferred. One or more of the phosphate groups of the oligonucleotide can be modified. In the case of partial modification, terminal groups are preferably modified, but oligonucleotides in which all the phosphate groups are modified are most preferred.

Preferred sugar modifications comprise replacement of one or more ribose residues of the oligonucleotide by hexose (figure 2) or by amino acids (peptide nucleic acid, PNA, figure 2).

Modifications of the bases comprise the use of 5-propinyl-uracyl, 5-propinylcytosine and the tricyclic cytosine analogue phenoxazine.

The synthesis of modified oligonucleotides and further suitable ways of modification are described in the literature (cf., for example, E. Uhlmann, A. Peyman, loc. cit.; M.D. Matteucci, R.W. Wagner, loc. cit.).

The oligonucleotides according to the invention can moreover be protected against degradation by exo-nucleases by terminal 3'-3' and/or 5'-5' internucleotide bonds (H. Seliger et al., Nucleosides & Nucleotides **10** (1-3), 469-477 (1991)).

The oligonucleotides according to the invention can furthermore additionally be substituted by groups which promote intracellular uptake, which serve *in vivo* or *in vitro* as reporter groups, and/or groups which, during hybridization of the oligoribonucleotide on the target RNA, attack the same by bonding or cleavage.

Examples of groups which promote intracellular uptake are lipophilic residues, such as alkyl residues, for example having 1 to 18 C atoms, cholesteryl or thiocholesteryl groups (E. Uhlmann, A. Peyman, loc. cit.) or conjugates which utilise natural carrier systems, such as e.g. bile acid or peptides for the corresponding receptor (e.g. receptor-mediated endocytosis).

Examples of reporter groups are fluorescent groups (e.g. acridinyl, dansyl or fluorescinyl groups) or chemiluminescent groups, such as e.g. acridinium ester groups.

Examples of oligonucleotide conjugates which bond to and/or cleave nucleic acids are to be found in E. Uhlmann, A. Peyman, loc. cit. Conjugate partners are, inter alia, acridine, psolaren, chloroethylaminoaryl, phenanthridine, azidophenacyl, azidoproflavine, phenazine, phenanthroline/Cu, porphyrin/Fe, benzo[e]pyridoindole and EDTA/Fe (Mergny et al., Science **256** (1992) 1681).

The oligonucleotides according to the invention are prepared in a manner known per se (cf. e.g. E. Uhlmann, A. Peyman, loc. cit.). Synthesis on a solid phase with the aid of an automatic synthesis apparatus is preferred.

To prepare medicaments, the oligonucleotides according to the invention are combined with conventional carrier substances, auxiliaries and/or additives. The oligonucleotides are suitable for systemic, local, subcutaneous, intrathecal and topical use and for administration by enema. For this, they can be used as a solution in suitable solvents, preferably aqueous solutions, in the form of liposomes, as an emulsion or in solid form, for example as a powder or in microencapsulated form.

The amount of oligonucleotides in the medicaments depends on the desired use and is preferably adjusted such that an administration of 0.001 to 100 mg oligonucleotide per kg of body weight, preferably 0.001 to 10 mg/kg of body weight, particularly preferably 0.01 to 3 mg/kg of body weight is achieved. Treatment is preferably carried out by repeated use over a period of one day to 6 weeks in a dose of preferably 0.01 to 3 mg/kg per day.

The oligonucleotides according to the invention are suitable for treating pathological conditions accompanied by an increased cell proliferation, in particular for treatment of benign and malignant tumours, such as testicular tumours, lymphomas, gastric carcinomas, bladder carcinomas, mammary carcinomas, bronchial carcinomas, sarcomas, renal carcinomas and melanomas, autoimmune

diseases, cicatrization, inflammations, allergies, rheumatic diseases and rejection reactions in case of transplantations.

A particular advantage of the oligonucleotides according to the invention is to be seen in that they allow treatment of tumours which are resistant to conventional chemotherapeutics. Such resistances arise either secondarily, i.e. after several administrations, with non-specific cytostatics, such as, for example, vinblastin or cisplatin, or are already primarily present with certain tumours, such as, for example, renal carcinoma.

The finding that the oligonucleotides according to the invention not only inhibit the growth of cells but also have a cytotoxic action, i.e. lead to the death of the treated tumour cells, was particularly surprising. The cytotoxic action in general starts after a treatment time of about 5 to 12 days. A treatment time of some months may be necessary for complete destruction of all the proliferating cells, whereby the treatment time may be interrupted by periods of non-treatment.

The invention is explained in more detail with the following examples.

Example 1

Action on the growth of RT4 cells in the multicellular spheroid test

The action of oligonucleotides according to the invention on bladder carcinoma cells of the cell line RT4 was investigated on multicellular spheroids and compared with corresponding sense and missense strands as a control.

For this, 2'-deoxyoligonucleotides with the following sequences were prepared in a known manner (Uhlmann and Peyman, loc. cit.):

start-2-anti	5'-ACC AGG CGT CTC GTG GGC CAC AT
start-2-sense	5'-ATG TGG CCC ACG AGA CGC CTG GT
missense	5'-AGT ACT CAG TAA CGC CTA CGG TAA G

Unless stated otherwise, all the oligonucleotides were employed in thiolated form, i.e. one oxygen atom of the phosphoric acid radicals was replaced by a sulphur atom.

Multicellular spheroids of the cell line RT-4 (ATCC no.: HTB2) were prepared by the method of Carlsson & Yuhas (J. Carlsson and J.M. Yuhas, Liquid-overlay culture of cellular spheroids, Recent Results in Cancer Research **95**; 1-23, 1984). After four days the multicellular spheroids showed a spherical morphology with a pronounced, sharp demarcation. The RT4 multicellular spheroids were then incubated in the presence of 120 µmol/l of the particular oligonucleotides in culture media at 37ºC with 5% CO_2 and the change in the spheroid diameter was measured. The oligonucleotides were introduced into the medium directly after the period of time necessary for formation of the spheroids. On the one hand a sample to which no oligonucleotides were added (control) and on the other hand the missense and sense oligonucleotide samples served as negative controls. Thereafter, the diameter of the multicellular spheroids was measured at intervals of 2 days. Three identical batches were investigated per test and the mean was then obtained. The results are plotted as a graph in figure 3.

An increase in the spheroid diameter to 132% of the starting value was observed in the control, while the addition of the thiolated missense oligonucleotide caused a stop in growth. The addition of the sense oligodeoxynucleotide caused a slight reduction in the spheroid diameter to 90%, while the antisense oligonucleotide led to a rapid decrease in the spheroid diameter down to complete dissolution of the spheroid on the 12th day of incubation.

After co-incubation of the multicellular spheroids with oligonucleotides, these were furthermore tested in respect of their vitality with the aid of fluorescent dyes. The dyes used for this were fluorescein-labelled disodium acetate (FITC-FDA) and propidium iodide (PI). Each multicellular spheroid was incubated with 2 µl FITC-FDA in a concentration of 1 µmol/l for 20 minutes and with 10 µl PI (concentration: 20 µg/ml) for 10 minutes. Under a fluorescence microscope living cells appear green due to the FITC-FDA staining and dead cells appear red due to the PI staining. A pronounced cytotoxic reaction of the cells investigated in the antisense-treated group was found.

The results show that the antisense oligonucleotide according to the invention is cytotoxic to the tumour cell line tested and causes irreversible cell damage, which leads to death of the cell.

To rule out the solvent alone having an influence on growth, corresponding control experiments were carried out with the solvent (solvent; only the solvent of the oligonucleotides, but not the oligonucleotides themselves, was added), which showed that this influencing parameter was to be ignored (cf. figure 4).

Example 2

Action on the growth of RT4 cells by microinjection

The action of the oligonucleotides mentioned in example 1 on RT4 cells by direct injection of the compounds into the cell was investigated. The oligonucleotides were employed in non-modified (non-thiolated) form for this experiment. By this test, on the one hand the activity of non-modified oligonucleotides is to be demonstrated, and on the other hand non-specific binding of the oligodeoxynucleotides to cell membrane receptors being responsible for the effects described in example 1 is to be ruled out.

RT4 cells were sown on special cover glasses (CELLocate® cover glasses, Eppendorf). A grid etched into the centre of these cover glasses facilitates finding the injected cells again. Before the cells were sown the cover glasses were placed in Petri dishes with a diameter of 3.5 cm and wetted with in each case 1 µl fibronectin, which ensures better attachment of the cells. 1.5×10^5 cells, which had been dissolved beforehand by means of trypsin, were then sown per dish in 2.5 ml supplemented RPMI 1640 medium and were cultured at 37ºC overnight in an incubating cabinet.

The microinjection was carried out with the aid of a transjector 5246 and micromanipulator 5171 (Eppendorf) under light microscope control (inverse microscope type Leitz DMIL, Leica). The microinjection capillaries were filled with in each case 2.0 µl oligonucleotide solution (concentration 120 µmol/l) with the aid of Mikroloader® pipette tips (Eppendorf). The concentration was adjusted with sterile-filtered phosphate-buffered saline solution (PBS). To check the permeability of the filled capillaries, the clean function of the transjector was employed under microscopic control. With the capillary open, after immersion into the culture medium a uniform outflow of injection liquid was observed. The injection pressure was set empirically at 130 hPa and corrected after the first injections such that the injection led to a clear increase in the size of the cell, without destroying it. The injection time was between 0.3 and 0.5 second.

For the cytoplasmic injections, the capillary tip was brought up to the cytoplasm until a reflection of light caused by pressure on the cell was to be observed. The capillary was then raised again a few µm and the automatic injection movement was triggered by pressing the button. During the injection the injection limit could be corrected upwards or downwards in 0.14 µm steps, so that irregularities in the cell substrate could be compensated. For comparative studies, microinjection capillaries which were drawn in one working operation were used in order to keep the amount

of liquid flowing out per injection as constant as possible for the same injection parameters. Nevertheless, the volume initiated varied from cell to cell, since the injection pressure and therefore the solution to be injected could spread out to a better or worse degree, depending on the region hit. To minimize the effects of cooling and a pH shift of the culture medium on the growth behaviour of the cells, the total injection time per cell culture dish was limited to 15 minutes.

The results of the test are plotted as a graph in fig. 5. It was found that injection of antisense oligonucleotides and a subsequent incubation time of 22 hours resulted in a loss of adhesion in approx. 70% of the cells. Since only living cells remain adhered to the cover glass, this result is to be equated with death of 70% of the cells. Injection of the sense or missense oligonucleotides led only to a loss of adhesion in 30% of the cells in each case, and sole injection of the solvent (PBS) led to a loss of adhesion in 10% of the cells.

Example 3

Action on the growth of J82 cells

The action of the oligonucleotides on the human bladder tumour cells line J82 was investigated analogously to example 1. The thiolated antisense oligonucleotide in a concentration of 120 µmol/l led to a decrease in the spheroid diameter by 20% after 11 days, while the spheroid diameter of the control increased by about 30% in the same period of time (fig. 6).

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Forschungszentrum Borstel
(B) STREET: Parkallee 1-40
(C) CITY: Borstel
(D) State: Schleswig-Holstein
(E) COUNTRY: Germany
(F) POSTAL CODE: D 23845

(ii) TITLE OF INVENTION: Antisense-Oligonucleotides for treating proliferating cells

(iii) NUMBER OF SEQUENCES: 3

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPA)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENZ CHARACTERISTICS:
(A) LENGTH: 12493 base pairs
(B) TYPE: Nucleotid
(C) STRANDEDNESS: dopple strand
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNS

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 197..9964

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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CTACCGGGCG GAGGTGAGCG CGGCGCCGGC TCCTCCTGCG GCGGACTTTG GTGCGACTT      60

GACGAGCGGT GGTTCGACAA GTGGCCTTGC GGGCCGGATC GTCCCAGTGG AAGAGTTGTA     120

AATTTGCTTC TGGCCTTCCC CTACGGATTA TACCTGGCCT TCCCCTACGG ATTATACTCA     180

ACTTACTGTT TAGAAA ATG TGG CCC ACG AGA CGC CTG GTT ACT ATC AAA          229
                  Met Trp Pro Thr Arg Arg Leu Val Thr Ile Lys
                    1               5                  10

AGG AGC GGG GTC GAC GGT CCC CAC TTT CCC CTG AGC CTC AGC ACC TGC       277
Arg Ser Gly Val Asp Gly Pro His Phe Pro Leu Ser Leu Ser Thr Cys
             15                  20                  25

TTG TTT GGA AGG GGT ATT GAA TGT GAC ATC CGT ATC CAG CTT CCT GTT       325
Leu Phe Gly Arg Gly Ile Glu Cys Asp Ile Arg Ile Gln Leu Pro Val
         30                  35                  40

GTG TCA AAA CAA CAT TGC AAA GTT GAA ATC CAT GAG CAG GAG GCA ATA       373
Val Ser Lys Gln His Cys Lys Val Glu Ile His Glu Gln Glu Ala Ile
     45                  50                  55
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TTA CAT AAT TTC AGT TCC ACA AAT CCA ACA CAA GTA AAT GGG TCT GTT      421
Leu His Asn Phe Ser Ser Thr Asn Pro Thr Gln Val Asn Gly Ser Val
 60                 65                  70                  75

ATT GAT GAG CCT GTA CGG CTA AAA CAT GGA GAT GTA ATA ACT ATT ATT      469
Ile Asp Glu Pro Val Arg Leu Lys His Gly Asp Val Ile Thr Ile Ile
                 80                  85                  90

GAT CGT TCC TTC AGG TAT GAA AAT GAA AGT CTT CAG AAT GGA AGG AAG      517
Asp Arg Ser Phe Arg Tyr Glu Asn Glu Ser Leu Gln Asn Gly Arg Lys
             95                 100                 105

TCA ACT GAA TTT CCA AGA AAA ATA CGT GAA CAG GAG CCA GCA CGT CGT      565
Ser Thr Glu Phe Pro Arg Lys Ile Arg Glu Gln Glu Pro Ala Arg Arg
    110                 115                 120

GTC TCA AGA TCT AGC TTC TCT TCT GAC CCT GAT GAG AAA GCT CAA GAT      613
Val Ser Arg Ser Ser Phe Ser Ser Asp Pro Asp Glu Lys Ala Gln Asp
    125                 130                 135

TCC AAG GCC TAT TCA AAA ATC ACT GAA GGA AAA GTT TCA GGA AAT CCT      661
Ser Lys Ala Tyr Ser Lys Ile Thr Glu Gly Lys Val Ser Gly Asn Pro
140                 145                 150                 155

CAG GTA CAT ATC AAG AAT GTC AAA GAA GAC AGT ACC GCA GAT GAC TCA      709
Gln Val His Ile Lys Asn Val Lys Glu Asp Ser Thr Ala Asp Asp Ser
                160                 165                 170

AAA GAC AGT GTT GCT CAG GGA ACA ACT AAT GTT CAT TCC TCA GAA CAT      757
Lys Asp Ser Val Ala Gln Gly Thr Thr Asn Val His Ser Ser Glu His
            175                 180                 185

GCT GGA CGT AAT GGC AGA AAT GCA GCT GAT CCC ATT TCT GGG GAT TTT      805
Ala Gly Arg Asn Gly Arg Asn Ala Ala Asp Pro Ile Ser Gly Asp Phe
        190                 195                 200

AAA GAA ATT TCC AGC GTT AAA TTA GTG AGC CGT TAT GGA GAA TTG AAG      853
Lys Glu Ile Ser Ser Val Lys Leu Val Ser Arg Tyr Gly Glu Leu Lys
    205                 210                 215

TCT GTT CCC ACT ACA CAA TGT CTT GAC AAT AGC AAA AAA AAT GAA TCT      901
Ser Val Pro Thr Thr Gln Cys Leu Asp Asn Ser Lys Lys Asn Glu Ser
220                 225                 230                 235

CCC TTT TGG AAG CTT TAT GAG TCA GTG AAG AAA GAG TTG GAT GTA AAA      949
Pro Phe Trp Lys Leu Tyr Glu Ser Val Lys Lys Glu Leu Asp Val Lys
                240                 245                 250

TCA CAA AAA GAA AAT GTC CTA CAG TAT TGT AGA AAA TCT GGA TTA CAA      997
Ser Gln Lys Glu Asn Val Leu Gln Tyr Cys Arg Lys Ser Gly Leu Gln
            255                 260                 265

ACT GAT TAC GCA ACA GAG AAA GAA AGT GCT GAT GGT TTA CAG GGG GAG     1045
Thr Asp Tyr Ala Thr Glu Lys Glu Ser Ala Asp Gly Leu Gln Gly Glu
        270                 275                 280

ACC CAA CTG TTG GTC TCG CGT AAG TCA AGA CCA AAA TCT GGT GGG AGC     1093
Thr Gln Leu Leu Val Ser Arg Lys Ser Arg Pro Lys Ser Gly Gly Ser
    285                 290                 295

GGC CAC GCT GTG GCA GAG CCT GCT TCA CCT GAA CAA GAG CTT GAC CAG     1141
Gly His Ala Val Ala Glu Pro Ala Ser Pro Glu Gln Glu Leu Asp Gln
300                 305                 310                 315
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AAC AAG GGG AAG GGA AGA GAC GTG GAG TCT GTT CAG ACT CCC AGC AAG      1189
Asn Lys Gly Lys Gly Arg Asp Val Glu Ser Val Gln Thr Pro Ser Lys
                320                 325                 330

GCT GTG GGC GCC AGC TTT CCT CTC TAT GAG CCG GCT AAA ATG AAG ACC      1237
Ala Val Gly Ala Ser Phe Pro Leu Tyr Glu Pro Ala Lys Met Lys Thr
            335                 340                 345

CCT GTA CAA TAT TCA CAG CAA CAA AAT TCT CCA CAA AAA CAT AAG AAC      1285
Pro Val Gln Tyr Ser Gln Gln Gln Asn Ser Pro Gln Lys His Lys Asn
        350                 355                 360

AAA GAC CTG TAT ACT ACT GGT AGA AGA GAA TCT GTG AAT CTG GGT AAA      1333
Lys Asp Leu Tyr Thr Thr Gly Arg Arg Glu Ser Val Asn Leu Gly Lys
    365                 370                 375

AGT GAA GGC TTC AAG GCT GGT GAT AAA ACT CTT ACT CCC AGG AAG CTT      1381
Ser Glu Gly Phe Lys Ala Gly Asp Lys Thr Leu Thr Pro Arg Lys Leu
380                 385                 390                 395

TCA ACT AGA AAT CGA ACA CCA GCT AAA GTT GAA GAT GCA GCT GAC TCT      1429
Ser Thr Arg Asn Arg Thr Pro Ala Lys Val Glu Asp Ala Ala Asp Ser
                400                 405                 410

GCC ACT AAG CCA GAA AAT CTC TCT TCC AAA ACC AGA GGA AGT ATT CCT      1477
Ala Thr Lys Pro Glu Asn Leu Ser Ser Lys Thr Arg Gly Ser Ile Pro
            415                 420                 425

ACA GAT GTG GAA GTT CTG CCT ACG GAA ACT GAA ATT CAC AAT GAG CCA      1525
Thr Asp Val Glu Val Leu Pro Thr Glu Thr Glu Ile His Asn Glu Pro
        430                 435                 440

TTT TTA ACT CTG TGG CTC ACT CAA GTT GAG AGG AAG ATC CAA AAG GAT      1573
Phe Leu Thr Leu Trp Leu Thr Gln Val Glu Arg Lys Ile Gln Lys Asp
    445                 450                 455

TCC CTC AGC AAG CCT GAG AAA TTG GGC ACT ACA GCT GGA CAG ATG TGC      1621
Ser Leu Ser Lys Pro Glu Lys Leu Gly Thr Thr Ala Gly Gln Met Cys
460                 465                 470                 475

TCT GGG TTA CCT GGT CTT AGT TCA GTT GAT ATC AAC AAC TTT GGT GAT      1669
Ser Gly Leu Pro Gly Leu Ser Ser Val Asp Ile Asn Asn Phe Gly Asp
                480                 485                 490

TCC ATT AAT GAG AGT GAG GGA ATA CCT TTG AAA AGA AGG CGT GTG TCC      1717
Ser Ile Asn Glu Ser Glu Gly Ile Pro Leu Lys Arg Arg Arg Val Ser
            495                 500                 505

TTT GGT GGG CAC CTA AGA CCT GAA CTA TTT GAT GAA AAC TTG CCT CCT      1765
Phe Gly Gly His Leu Arg Pro Glu Leu Phe Asp Glu Asn Leu Pro Pro
        510                 515                 520

AAT ACG CCT CTC AAA AGG GGA GAA GCC CCA ACC AAA AGA AAG TCT CTG      1813
Asn Thr Pro Leu Lys Arg Gly Glu Ala Pro Thr Lys Arg Lys Ser Leu
    525                 530                 535

GTA ATG CAC ACT CCA CCT GTC CTG AAG AAA ATC ATC AAG GAA CAG CCT      1861
Val Met His Thr Pro Pro Val Leu Lys Lys Ile Ile Lys Glu Gln Pro
540                 545                 550                 555

CAA CCA TCA GGA AAA CAA GAG TCA GGT TCA GAA ATC CAT GTG GAA GTG      1909
Gln Pro Ser Gly Lys Gln Glu Ser Gly Ser Glu Ile His Val Glu Val
                560                 565                 570
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AAG GCA CAA AGC TTG GTT ATA AGC CCT CCA GCT CCT AGT CCT AGG AAA     1957
Lys Ala Gln Ser Leu Val Ile Ser Pro Pro Ala Pro Ser Pro Arg Lys
            575                 580                 585

ACT CCA GTT GCC AGT GAT CAA CGC CGT AGG TCC TGC AAA ACA GCC CCT     2005
Thr Pro Val Ala Ser Asp Gln Arg Arg Arg Ser Cys Lys Thr Ala Pro
        590                 595                 600

GCT TCC AGC AGC AAA TCT CAG ACA GAG GTT CCT AAG AGA GGA GGA GAA     2053
Ala Ser Ser Ser Lys Ser Gln Thr Glu Val Pro Lys Arg Gly Gly Glu
    605                 610                 615

AGA GTG GCA ACC TGC CTT CAA AAG AGA GTG TCT ATC AGC CGA AGT CAA     2101
Arg Val Ala Thr Cys Leu Gln Lys Arg Val Ser Ile Ser Arg Ser Gln
620                 625                 630                 635

CAT GAT ATT TTA CAG ATG ATA TGT TCC AAA AGA AGA AGT GGT GCT TCG     2149
His Asp Ile Leu Gln Met Ile Cys Ser Lys Arg Arg Ser Gly Ala Ser
                640                 645                 650

GAA GCA AAT CTG ATT GTT GCA AAA TCA TGG GCA GAT GTA GTA AAA CTT     2197
Glu Ala Asn Leu Ile Val Ala Lys Ser Trp Ala Asp Val Val Lys Leu
            655                 660                 665

GGT GCA AAA CAA ACA CAA ACT AAA GTC ATA AAA CAT GGT CCT CAA AGG     2245
Gly Ala Lys Gln Thr Gln Thr Lys Val Ile Lys His Gly Pro Gln Arg
        670                 675                 680

TCA ATG AAC AAA AGG CAA AGA AGA CCT GCT ACT CCA AAG AAG CCT GTG     2293
Ser Met Asn Lys Arg Gln Arg Arg Pro Ala Thr Pro Lys Lys Pro Val
    685                 690                 695

GGC GAA GTT CAC AGT CAA TTT AGT ACA GGC CAC GCA AAC TCT CCT TGT     2341
Gly Glu Val His Ser Gln Phe Ser Thr Gly His Ala Asn Ser Pro Cys
700                 705                 710                 715

ACC ATA ATA ATA GGG AAA GCT CAT ACT GAA AAA GTA CAT GTG CCT GCT     2389
Thr Ile Ile Ile Gly Lys Ala His Thr Glu Lys Val His Val Pro Ala
                720                 725                 730

CGA CCC TAC AGA GTG CTC AAC AAC TTC ATT TCC AAC CAA AAA ATG GAC     2437
Arg Pro Tyr Arg Val Leu Asn Asn Phe Ile Ser Asn Gln Lys Met Asp
            735                 740                 745

TTT AAG GAA GAT CTT TCA GGA ATA GCT GAA ATG TTC AAG ACC CCA GTG     2485
Phe Lys Glu Asp Leu Ser Gly Ile Ala Glu Met Phe Lys Thr Pro Val
        750                 755                 760

AAG GAG CAA CCG CAG TTG ACA AGC ACA TGT CAC ATC GCT ATT TCA AAT     2533
Lys Glu Gln Pro Gln Leu Thr Ser Thr Cys His Ile Ala Ile Ser Asn
    765                 770                 775

TCA GAG AAT TTG CTT GGA AAA CAG TTT CAA GGA ACT GAT TCA GGA GAA     2581
Ser Glu Asn Leu Leu Gly Lys Gln Phe Gln Gly Thr Asp Ser Gly Glu
780                 785                 790                 795

GAA CCT CTG CTC CCC ACC TCA GAG AGT TTT GGA GGA AAT GTG TTC TTC     2629
Glu Pro Leu Leu Pro Thr Ser Glu Ser Phe Gly Gly Asn Val Phe Phe
                800                 805                 810

AGT GCA CAG AAT GCA GCA AAA CAG CCA TCT GAT AAA TGC TCT GCA AGC     2677
Ser Ala Gln Asn Ala Ala Lys Gln Pro Ser Asp Lys Cys Ser Ala Ser
            815                 820                 825
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CCT CCC TTA AGA CGG CAG TGT ATT AGA GAA AAT GGA AAC GTA GCA AAA      2725
Pro Pro Leu Arg Arg Gln Cys Ile Arg Glu Asn Gly Asn Val Ala Lys
        830                 835                 840

ACG CCC AGG AAC ACC TAC AAA ATG ACT TCT CTG GAG ACA AAA ACT TCA      2773
Thr Pro Arg Asn Thr Tyr Lys Met Thr Ser Leu Glu Thr Lys Thr Ser
    845                 850                 855

GAT ACT GAG ACA GAG CCT TCA AAA ACA GTA TCC ACT GTA AAC AGG TCA      2821
Asp Thr Glu Thr Glu Pro Ser Lys Thr Val Ser Thr Val Asn Arg Ser
860                 865                 870                 875

GGA AGG TCT ACA GAG TTC AGG AAT ATA CAG AAG CTA CCT GTG GAA AGT      2869
Gly Arg Ser Thr Glu Phe Arg Asn Ile Gln Lys Leu Pro Val Glu Ser
                880                 885                 890

AAG AGT GAA GAA ACA AAT ACA GAA ATT GTT GAG TGC ATC CTA AAA AGA      2917
Lys Ser Glu Glu Thr Asn Thr Glu Ile Val Glu Cys Ile Leu Lys Arg
            895                 900                 905

GGT CAG AAG GCA ACA CTA CTA CAA CAA AGG AGA GAA GGA GAG ATG AAG      2965
Gly Gln Lys Ala Thr Leu Leu Gln Gln Arg Arg Glu Gly Glu Met Lys
        910                 915                 920

GAA ATA GAA AGA CCT TTT GAG ACA TAT AAG GAA AAT ATT GAA TTA AAA      3013
Glu Ile Glu Arg Pro Phe Glu Thr Tyr Lys Glu Asn Ile Glu Leu Lys
    925                 930                 935

GAA AAC GAT GAA AAG ATG AAA GCA ATG AAG AGA TCA AGA ACT TGG GGG      3061
Glu Asn Asp Glu Lys Met Lys Ala Met Lys Arg Ser Arg Thr Trp Gly
940                 945                 950                 955

CAG AAA TGT GCA CCA ATG TCT GAC CTG ACA GAC CTC AAG AGC TTG CCT      3109
Gln Lys Cys Ala Pro Met Ser Asp Leu Thr Asp Leu Lys Ser Leu Pro
                960                 965                 970

GAT ACA GAA CTC ATG AAA GAC ACG GCA CGT GGC CAG AAT CTC CTC CAA      3157
Asp Thr Glu Leu Met Lys Asp Thr Ala Arg Gly Gln Asn Leu Leu Gln
            975                 980                 985

ACC CAA GAT CAT GCC AAG GCA CCA AAG AGT GAG AAA GGC AAA ATC ACT      3205
Thr Gln Asp His Ala Lys Ala Pro Lys Ser Glu Lys Gly Lys Ile Thr
        990                 995                 1000

AAA ATG CCC TGC CAG TCA TTA CAA CCA GAA CCA ATA AAC ACC CCA ACA      3253
Lys Met Pro Cys Gln Ser Leu Gln Pro Glu Pro Ile Asn Thr Pro Thr
    1005                1010                1015

CAC ACA AAA CAA CAG TTG AAG GCA TCC CTG GGG AAA GTA GGT GTG AAA      3301
His Thr Lys Gln Gln Leu Lys Ala Ser Leu Gly Lys Val Gly Val Lys
1020                1025                1030                1035

GAA GAG CTC CTA GCA GTC GGC AAG TTC ACA CGG ACG TCA GGG GAG ACC      3349
Glu Glu Leu Leu Ala Val Gly Lys Phe Thr Arg Thr Ser Gly Glu Thr
                1040                1045                1050

ACG CAC ACG CAC AGA GAG CCA GCA GGA GAT GGC AAG AGC ATC AGA ACG      3397
Thr His Thr His Arg Glu Pro Ala Gly Asp Gly Lys Ser Ile Arg Thr
            1055                1060                1065

TTT AAG GAG TCT CCA AAG CAG ATC CTG GAC CCA GCA GCC CGT GTA ACT      3445
Phe Lys Glu Ser Pro Lys Gln Ile Leu Asp Pro Ala Ala Arg Val Thr
        1070                1075                1080
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GGA ATG AAG AAG TGG CCA AGA ACG CCT AAG GAA GAG GCC CAG TCA CTA      3493
Gly Met Lys Lys Trp Pro Arg Thr Pro Lys Glu Glu Ala Gln Ser Leu
     1085                1090                1095

GAA GAC CTG GCT GGC TTC AAA GAG CTC TTC CAG ACA CCA GGT CCC TCT      3541
Glu Asp Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr Pro Gly Pro Ser
1100                1105                1110                1115

GAG GAA TCA ATG ACT GAT GAG AAA ACT ACC AAA ATA GCC TGC AAA TCT      3589
Glu Glu Ser Met Thr Asp Glu Lys Thr Thr Lys Ile Ala Cys Lys Ser
                1120                1125                1130

CCA CCA CCA GAA TCA GTG GAC ACT CCA ACA AGC ACA AAG CAA TGG CCT      3637
Pro Pro Pro Glu Ser Val Asp Thr Pro Thr Ser Thr Lys Gln Trp Pro
          1135                1140                1145

AAG AGA AGT CTC AGG AAA GCA GAT GTA GAG GAA GAA TTC TTA GCA CTC      3685
Lys Arg Ser Leu Arg Lys Ala Asp Val Glu Glu Glu Phe Leu Ala Leu
     1150                1155                1160

AGG AAA CTA ACA CCA TCA GCA GGG AAA GCC ATG CTT ACG CCC AAA CCA      3733
Arg Lys Leu Thr Pro Ser Ala Gly Lys Ala Met Leu Thr Pro Lys Pro
1165                1170                1175

GCA GGA GGT GAT GAG AAA GAC ATT AAA GCA TTT ATG GGA ACT CCA GTG      3781
Ala Gly Gly Asp Glu Lys Asp Ile Lys Ala Phe Met Gly Thr Pro Val
1180                1185                1190                1195

CAG AAA CTG GAC CTG GCA GGA ACT TTA CCT GGC AGC AAA AGA CAG CTA      3829
Gln Lys Leu Asp Leu Ala Gly Thr Leu Pro Gly Ser Lys Arg Gln Leu
                1200                1205                1210

CAG ACT CCT AAG GAA AAG GCC CAG GCT CTA GAA GAC CTG GCT GGC TTT      3877
Gln Thr Pro Lys Glu Lys Ala Gln Ala Leu Glu Asp Leu Ala Gly Phe
          1215                1220                1225

AAA GAG CTC TTC CAG ACT CCT GGT CAC ACC GAG GAA TTA GTG GCT GCT      3925
Lys Glu Leu Phe Gln Thr Pro Gly His Thr Glu Glu Leu Val Ala Ala
     1230                1235                1240

GGT AAA ACC ACT AAA ATA CCC TGC GAC TCT CCA CAG TCA GAC CCA GTG      3973
Gly Lys Thr Thr Lys Ile Pro Cys Asp Ser Pro Gln Ser Asp Pro Val
1245                1250                1255

GAC ACC CCA ACA AGC ACA AAG CAA CGA CCC AAG AGA AGT ATC AGG AAA      4021
Asp Thr Pro Thr Ser Thr Lys Gln Arg Pro Lys Arg Ser Ile Arg Lys
1260                1265                1270                1275

GCA GAT GTA GAG GGA GAA CTC TTA GCG TGC AGG AAT CTA ATG CCA TCA      4069
Ala Asp Val Glu Gly Glu Leu Leu Ala Cys Arg Asn Leu Met Pro Ser
                1280                1285                1290

GCA GGC AAA GCC ATG CAC ACG CCT AAA CCA TCA GTA GGT GAA GAG AAA      4117
Ala Gly Lys Ala Met His Thr Pro Lys Pro Ser Val Gly Glu Glu Lys
          1295                1300                1305

GAC ATC ATC ATA TTT GTG GGA ACT CCA GTG CAG AAA CTG GAC CTG ACA      4165
Asp Ile Ile Ile Phe Val Gly Thr Pro Val Gln Lys Leu Asp Leu Thr
     1310                1315                1320

GAG AAC TTA ACC GGC AGC AAG AGA CGG CCA CAA ACT CCT AAG GAA GAG      4213
Glu Asn Leu Thr Gly Ser Lys Arg Arg Pro Gln Thr Pro Lys Glu Glu
1325                1330                1335
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GCC CAG GCT CTG GAA GAC CTG ACT GGC TTT AAA GAG CTC TTC CAG ACC      4261
Ala Gln Ala Leu Glu Asp Leu Thr Gly Phe Lys Glu Leu Phe Gln Thr
1340                 1345                 1350                 1355

CCT GGT CAT ACT GAA GAA GCA GTG GCT GCT GGC AAA ACT ACT AAA ATG      4309
Pro Gly His Thr Glu Glu Ala Val Ala Ala Gly Lys Thr Thr Lys Met
                1360                 1365                 1370

CCC TGC GAA TCT TCT CCA CCA GAA TCA GCA GAC ACC CCA ACA AGC ACA      4357
Pro Cys Glu Ser Ser Pro Pro Glu Ser Ala Asp Thr Pro Thr Ser Thr
            1375                 1380                 1385

AGA AGG CAG CCC AAG ACA CCT TTG GAG AAA AGG GAC GTA CAG AAG GAG      4405
Arg Arg Gln Pro Lys Thr Pro Leu Glu Lys Arg Asp Val Gln Lys Glu
        1390                 1395                 1400

CTC TCA GCC CTG AAG AAG CTC ACA CAG ACA TCA GGG GAA ACC ACA CAC      4453
Leu Ser Ala Leu Lys Lys Leu Thr Gln Thr Ser Gly Glu Thr Thr His
    1405                 1410                 1415

ACA GAT AAA GTA CCA GGA GGT GAG GAT AAA AGC ATC AAC GCG TTT AGG      4501
Thr Asp Lys Val Pro Gly Gly Glu Asp Lys Ser Ile Asn Ala Phe Arg
1420                 1425                 1430                 1435

GAA ACT GCA AAA CAG AAA CTG GAC CCA GCA GCA AGT GTA ACT GGT AGC      4549
Glu Thr Ala Lys Gln Lys Leu Asp Pro Ala Ala Ser Val Thr Gly Ser
                1440                 1445                 1450

AAG AGG CAC CCA AAA ACT AAG GAA AAG GCC CAA CCC CTA GAA GAC CTG      4597
Lys Arg His Pro Lys Thr Lys Glu Lys Ala Gln Pro Leu Glu Asp Leu
            1455                 1460                 1465

GCT GGC TGG AAA GAG CTC TTC CAG ACA CCA GTA TGC ACT GAC AAG CCC      4645
Ala Gly Trp Lys Glu Leu Phe Gln Thr Pro Val Cys Thr Asp Lys Pro
        1470                 1475                 1480

ACG ACT CAC GAG AAA ACT ACC AAA ATA GCC TGC AGA TCA CAA CCA GAC      4693
Thr Thr His Glu Lys Thr Thr Lys Ile Ala Cys Arg Ser Gln Pro Asp
    1485                 1490                 1495

CCA GTG GAC ACA CCA ACA AGC TCC AAG CCA CAG TCC AAG AGA AGT CTC      4741
Pro Val Asp Thr Pro Thr Ser Ser Lys Pro Gln Ser Lys Arg Ser Leu
1500                 1505                 1510                 1515

AGG AAA GTG GAC GTA GAA GAA GAA TTC TTC GCA CTC AGG AAA CGA ACA      4789
Arg Lys Val Asp Val Glu Glu Glu Phe Phe Ala Leu Arg Lys Arg Thr
                1520                 1525                 1530

CCA TCA GCA GGC AAA GCC ATG CAC ACA CCC AAA CCA GCA GTA AGT GGT      4837
Pro Ser Ala Gly Lys Ala Met His Thr Pro Lys Pro Ala Val Ser Gly
            1535                 1540                 1545

GAG AAA AAC ATC TAC GCA TTT ATG GGA ACT CCA GTG CAG AAA CTG GAC      4885
Glu Lys Asn Ile Tyr Ala Phe Met Gly Thr Pro Val Gln Lys Leu Asp
        1550                 1555                 1560

CTG ACA GAG AAC TTA ACT GGC AGC AAG AGA CGG CTA CAA ACT CCT AAG      4933
Leu Thr Glu Asn Leu Thr Gly Ser Lys Arg Arg Leu Gln Thr Pro Lys
    1565                 1570                 1575

GAA AAG GCC CAG GCT CTA GAA GAC CTG GCT GGC TTT AAA GAG CTC TTC      4981
Glu Lys Ala Gln Ala Leu Glu Asp Leu Ala Gly Phe Lys Glu Leu Phe
1580                 1585                 1590                 1595
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CAG ACA CGA GGT CAC ACT GAG GAA TCA ATG ACT AAC GAT AAA ACT GCC      5029
Gln Thr Arg Gly His Thr Glu Glu Ser Met Thr Asn Asp Lys Thr Ala
                1600                1605                1610

AAA GTA GCC TGC AAA TCT TCA CAA CCA GAC CTA GAC AAA AAC CCA GCA      5077
Lys Val Ala Cys Lys Ser Ser Gln Pro Asp Leu Asp Lys Asn Pro Ala
           1615                1620                1625

AGC TCC AAG CGA CGG CTC AAG ACA TCC CTG GGG AAA GTG GGC GTG AAA      5125
Ser Ser Lys Arg Arg Leu Lys Thr Ser Leu Gly Lys Val Gly Val Lys
      1630                1635                1640

GAA GAG CTC CTA GCA GTT GGC AAG CTC ACA CAG ACA TCA GGA GAG ACT      5173
Glu Glu Leu Leu Ala Val Gly Lys Leu Thr Gln Thr Ser Gly Glu Thr
 1645                1650                1655

ACA CAC ACA CAC ACA GAG CCA ACA GGA GAT GGT AAG AGC ATG AAA GCA      5221
Thr His Thr His Thr Glu Pro Thr Gly Asp Gly Lys Ser Met Lys Ala
1660                1665                1670                1675

TTT ATG GAG TCT CCA AAG CAG ATC TTA GAC TCA GCA GCA AGT CTA ACT      5269
Phe Met Glu Ser Pro Lys Gln Ile Leu Asp Ser Ala Ala Ser Leu Thr
                1680                1685                1690

GGC AGC AAG AGG CAG CTG AGA ACT CCT AAG GGA AAG TCT GAA GTC CCT      5317
Gly Ser Lys Arg Gln Leu Arg Thr Pro Lys Gly Lys Ser Glu Val Pro
           1695                1700                1705

GAA GAC CTG GCC GGC TTC ATC GAG CTC TTC CAG ACA CCA AGT CAC ACT      5365
Glu Asp Leu Ala Gly Phe Ile Glu Leu Phe Gln Thr Pro Ser His Thr
      1710                1715                1720

AAG GAA TCA ATG ACT AAT GAA AAA ACT ACC AAA GTA TCC TAC AGA GCT      5413
Lys Glu Ser Met Thr Asn Glu Lys Thr Thr Lys Val Ser Tyr Arg Ala
 1725                1730                1735

TCA CAG CCA GAC CTA GTG GAC ACC CCA ACA AGC TCC AAG CCA CAG CCC      5461
Ser Gln Pro Asp Leu Val Asp Thr Pro Thr Ser Ser Lys Pro Gln Pro
1740                1745                1750                1755

AAG AGA AGT CTC AGG AAA GCA GAC ACT GAA GAA GAA TTT TTA GCA TTT      5509
Lys Arg Ser Leu Arg Lys Ala Asp Thr Glu Glu Glu Phe Leu Ala Phe
                1760                1765                1770

AGG AAA CAA ACG CCA TCA GCA GGC AAA GCC ATG CAC ACA CCC AAA CCA      5557
Arg Lys Gln Thr Pro Ser Ala Gly Lys Ala Met His Thr Pro Lys Pro
           1775                1780                1785

GCA GTA GGT GAA GAG AAA GAC ATC AAC ACG TTT TTG GGA ACT CCA GTG      5605
Ala Val Gly Glu Glu Lys Asp Ile Asn Thr Phe Leu Gly Thr Pro Val
      1790                1795                1800

CAG AAA CTG GAC CAG CCA GGA AAT TTA CCT GGC AGC AAT AGA CGG CTA      5653
Gln Lys Leu Asp Gln Pro Gly Asn Leu Pro Gly Ser Asn Arg Arg Leu
 1805                1810                1815

CAA ACT CGT AAG GAA AAG GCC CAG GCT CTA GAA GAA CTG ACT GGC TTC      5701
Gln Thr Arg Lys Glu Lys Ala Gln Ala Leu Glu Glu Leu Thr Gly Phe
1820                1825                1830                1835

AGA GAG CTT TTC CAG ACA CCA TGC ACT GAT AAC CCC ACA GCT GAT GAG      5749
Arg Glu Leu Phe Gln Thr Pro Cys Thr Asp Asn Pro Thr Ala Asp Glu
                1840                1845                1850
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AAA ACT ACC AAA AAA ATA CTC TGC AAA TCT CCG CAA TCA GAC CCA GCG      5797
Lys Thr Thr Lys Lys Ile Leu Cys Lys Ser Pro Gln Ser Asp Pro Ala
            1855                1860                1865

GAC ACC CCA ACA AAC ACA AAG CAA CGG CCC AAG AGA AGC CTC AAG AAA      5845
Asp Thr Pro Thr Asn Thr Lys Gln Arg Pro Lys Arg Ser Leu Lys Lys
        1870                1875                1880

GCA GAC GTA GAG GAA GAA TTT TTA GCA TTC AGG AAA CTA ACA CCA TCA      5893
Ala Asp Val Glu Glu Glu Phe Leu Ala Phe Arg Lys Leu Thr Pro Ser
    1885                1890                1895

GCA GGC AAA GCC ATG CAC ACG CCT AAA GCA GCA GTA GGT GAA GAG AAA      5941
Ala Gly Lys Ala Met His Thr Pro Lys Ala Ala Val Gly Glu Glu Lys
1900                1905                1910                1915

GAC ATC AAC ACA TTT GTG GGG ACT CCA GTG GAG AAA CTG GAC CTG CTA      5989
Asp Ile Asn Thr Phe Val Gly Thr Pro Val Glu Lys Leu Asp Leu Leu
                1920                1925                1930

GGA AAT TTA CCT GGC AGC AAG AGA CGG CCA CAA ACT CCT AAA GAA AAG      6037
Gly Asn Leu Pro Gly Ser Lys Arg Arg Pro Gln Thr Pro Lys Glu Lys
            1935                1940                1945

GCC AAG GCT CTA GAA GAT CTG GCT GGC TTC AAA GAG CTC TTC CAG ACA      6085
Ala Lys Ala Leu Glu Asp Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr
        1950                1955                1960

CCA GGT CAC ACT GAG GAA TCA ATG ACC GAT GAC AAA ATC ACA GAA GTA      6133
Pro Gly His Thr Glu Glu Ser Met Thr Asp Asp Lys Ile Thr Glu Val
    1965                1970                1975

TCC TGC AAA TCT CCA CAA CCA GAC CCA GTC AAA ACC CCA ACA AGC TCC      6181
Ser Cys Lys Ser Pro Gln Pro Asp Pro Val Lys Thr Pro Thr Ser Ser
1980                1985                1990                1995

AAG CAA CGA CTC AAG ATA TCC TTG GGG AAA GTA GGT GTG AAA GAA GAG      6229
Lys Gln Arg Leu Lys Ile Ser Leu Gly Lys Val Gly Val Lys Glu Glu
                2000                2005                2010

GTC CTA CCA GTC GGC AAG CTC ACA CAG ACG TCA GGG AAG ACC ACA CAG      6277
Val Leu Pro Val Gly Lys Leu Thr Gln Thr Ser Gly Lys Thr Thr Gln
            2015                2020                2025

ACA CAC AGA GAG ACA GCA GGA GAT GGA AAG AGC ATC AAA GCG TTT AAG      6325
Thr His Arg Glu Thr Ala Gly Asp Gly Lys Ser Ile Lys Ala Phe Lys
        2030                2035                2040

GAA TCT GCA AAG CAG ATG CTG GAC CCA GCA AAC TAT GGA ACT GGG ATG      6373
Glu Ser Ala Lys Gln Met Leu Asp Pro Ala Asn Tyr Gly Thr Gly Met
    2045                2050                2055

GAG AGG TGG CCA AGA ACA CCT AAG GAA GAG GCC CAA TCA CTA GAA GAC      6421
Glu Arg Trp Pro Arg Thr Pro Lys Glu Glu Ala Gln Ser Leu Glu Asp
2060                2065                2070                2075

CTG GCC GGC TTC AAA GAG CTC TTC CAG ACA CCA GAC CAC ACT GAG GAA      6469
Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr Pro Asp His Thr Glu Glu
                2080                2085                2090

TCA ACA ACT GAT GAC AAA ACT ACC AAA ATA GCC TGC AAA TCT CCA CCA      6517
Ser Thr Thr Asp Asp Lys Thr Thr Lys Ile Ala Cys Lys Ser Pro Pro
            2095                2100                2105
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CCA GAA TCA ATG GAC ACT CCA ACA AGC ACA AGG AGG CGG CCC AAA ACA      6565
Pro Glu Ser Met Asp Thr Pro Thr Ser Thr Arg Arg Arg Pro Lys Thr
        2110                2115                2120

CCT TTG GGG AAA AGG GAT ATA GTG GAA GAG CTC TCA GCC CTG AAG CAG      6613
Pro Leu Gly Lys Arg Asp Ile Val Glu Glu Leu Ser Ala Leu Lys Gln
    2125                2130                2135

CTC ACA CAG ACC ACA CAC ACA GAC AAA GTA CCA GGA GAT GAG GAT AAA      6661
Leu Thr Gln Thr Thr His Thr Asp Lys Val Pro Gly Asp Glu Asp Lys
2140                2145                2150                2155

GGC ATC AAC GTG TTC AGG GAA ACT GCA AAA CAG AAA CTG GAC CCA GCA      6709
Gly Ile Asn Val Phe Arg Glu Thr Ala Lys Gln Lys Leu Asp Pro Ala
                2160                2165                2170

GCA AGT GTA ACT GGT AGC AAG AGG CAG CCA AGA ACT CCT AAG GGA AAA      6757
Ala Ser Val Thr Gly Ser Lys Arg Gln Pro Arg Thr Pro Lys Gly Lys
            2175                2180                2185

GCC CAA CCC CTA GAA GAC TTG GCT GGC TTG AAA GAG CTC TTC CAG ACA      6805
Ala Gln Pro Leu Glu Asp Leu Ala Gly Leu Lys Glu Leu Phe Gln Thr
        2190                2195                2200

CCA GTA TGC ACT GAC AAG CCC ACG ACT CAC GAG AAA ACT ACC AAA ATA      6853
Pro Val Cys Thr Asp Lys Pro Thr Thr His Glu Lys Thr Thr Lys Ile
    2205                2210                2215

GCC TGC AGA TCT CCA CAA CCA GAC CCA GTG GGT ACC CCA ACA ATC TTC      6901
Ala Cys Arg Ser Pro Gln Pro Asp Pro Val Gly Thr Pro Thr Ile Phe
2220                2225                2230                2235

AAG CCA CAG TCC AAG AGA AGT CTC AGG AAA GCA GAC GTA GAG GAA GAA      6949
Lys Pro Gln Ser Lys Arg Ser Leu Arg Lys Ala Asp Val Glu Glu Glu
                2240                2245                2250

TCC TTA GCA CTC AGG AAA CGA ACA CCA TCA GTA GGG AAA GCT ATG GAC      6997
Ser Leu Ala Leu Arg Lys Arg Thr Pro Ser Val Gly Lys Ala Met Asp
            2255                2260                2265

ACA CCC AAA CCA GCA GGA GGT GAT GAG AAA GAC ATG AAA GCA TTT ATG      7045
Thr Pro Lys Pro Ala Gly Gly Asp Glu Lys Asp Met Lys Ala Phe Met
        2270                2275                2280

GGA ACT CCA GTG CAG AAA TTG GAC CTG CCA GGA AAT TTA CCT GGC AGC      7093
Gly Thr Pro Val Gln Lys Leu Asp Leu Pro Gly Asn Leu Pro Gly Ser
    2285                2290                2295

AAA AGA TGG CCA CAA ACT CCT AAG GAA AAG GCC CAG GCT CTA GAA GAC      7141
Lys Arg Trp Pro Gln Thr Pro Lys Glu Lys Ala Gln Ala Leu Glu Asp
2300                2305                2310                2315

CTG GCT GGC TTC AAA GAG CTC TTC CAG ACA CCA GGC ACT GAC AAG CCC      7189
Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr Pro Gly Thr Asp Lys Pro
                2320                2325                2330

ACG ACT GAT GAG AAA ACT ACC AAA ATA GCC TGC AAA TCT CCA CAA CCA      7237
Thr Thr Asp Glu Lys Thr Thr Lys Ile Ala Cys Lys Ser Pro Gln Pro
            2335                2340                2345

GAC CCA GTG GAC ACC CCA GCA AGC ACA AAG CAA CGG CCC AAG AGA AAC      7285
Asp Pro Val Asp Thr Pro Ala Ser Thr Lys Gln Arg Pro Lys Arg Asn
        2350                2355                2360
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CTC AGG AAA GCA GAC GTA GAG GAA GAA TTT TTA GCA CTC AGG AAA CGA      7333
Leu Arg Lys Ala Asp Val Glu Glu Glu Phe Leu Ala Leu Arg Lys Arg
    2365                2370                2375

ACA CCA TCA GCA GGC AAA GCC ATG GAC ACC CCA AAA CCA GCA GTA AGT      7381
Thr Pro Ser Ala Gly Lys Ala Met Asp Thr Pro Lys Pro Ala Val Ser
2380                2385                2390                2395

GAT GAG AAA AAT ATC AAC ACA TTT GTG GAA ACT CCA GTG CAG AAA CTG      7429
Asp Glu Lys Asn Ile Asn Thr Phe Val Glu Thr Pro Val Gln Lys Leu
                2400                2405                2410

GAC CTG CTA GGA AAT TTA CCT GGC AGC AAG AGA CAG CCA CAG ACT CCT      7477
Asp Leu Leu Gly Asn Leu Pro Gly Ser Lys Arg Gln Pro Gln Thr Pro
            2415                2420                2425

AAG GAA AAG GCT GAG GCT CTA GAG GAC CTG GTT GGC TTC AAA GAA CTC      7525
Lys Glu Lys Ala Glu Ala Leu Glu Asp Leu Val Gly Phe Lys Glu Leu
        2430                2435                2440

TTC CAG ACA CCA GGT CAC ACT GAG GAA TCA ATG ACT GAT GAC AAA ATC      7573
Phe Gln Thr Pro Gly His Thr Glu Glu Ser Met Thr Asp Asp Lys Ile
    2445                2450                2455

ACA GAA GTA TCC TGT AAA TCT CCA CAG CCA GAG TCA TTC AAA ACC TCA      7621
Thr Glu Val Ser Cys Lys Ser Pro Gln Pro Glu Ser Phe Lys Thr Ser
2460                2465                2470                2475

AGA AGC TCC AAG CAA AGG CTC AAG ATA CCC CTG GTG AAA GTG GAC ATG      7669
Arg Ser Ser Lys Gln Arg Leu Lys Ile Pro Leu Val Lys Val Asp Met
                2480                2485                2490

AAA GAA GAG CCC CTA GCA GTC AGC AAG CTC ACA CGG ACA TCA GGG GAG      7717
Lys Glu Glu Pro Leu Ala Val Ser Lys Leu Thr Arg Thr Ser Gly Glu
            2495                2500                2505

ACT ACG CAA ACA CAC ACA GAG CCA ACA GGA GAT AGT AAG AGC ATC AAA      7765
Thr Thr Gln Thr His Thr Glu Pro Thr Gly Asp Ser Lys Ser Ile Lys
        2510                2515                2520

GCG TTT AAG GAG TCT CCA AAG CAG ATC CTG GAC CCA GCA GCA AGT GTA      7813
Ala Phe Lys Glu Ser Pro Lys Gln Ile Leu Asp Pro Ala Ala Ser Val
    2525                2530                2535

ACT GGT AGC AGG AGG CAG CTG AGA ACT CGT AAG GAA AAG GCC CGT GCT      7861
Thr Gly Ser Arg Arg Gln Leu Arg Thr Arg Lys Glu Lys Ala Arg Ala
2540                2545                2550                2555

CTA GAA GAC CTG GTT GAC TTC AAA GAG CTC TTC TCA GCA CCA GGT CAC      7909
Leu Glu Asp Leu Val Asp Phe Lys Glu Leu Phe Ser Ala Pro Gly His
                2560                2565                2570

ACT GAA GAG TCA ATG ACT ATT GAC AAA AAC ACA AAA ATT CCC TGC AAA      7957
Thr Glu Glu Ser Met Thr Ile Asp Lys Asn Thr Lys Ile Pro Cys Lys
            2575                2580                2585

TCT CCC CCA CCA GAA CTA ACA GAC ACT GCC ACG AGC ACA AAG AGA TGC      8005
Ser Pro Pro Pro Glu Leu Thr Asp Thr Ala Thr Ser Thr Lys Arg Cys
        2590                2595                2600

CCC AAG ACA CGT CCC AGG AAA GAA GTA AAA GAG GAG CTC TCA GCA GTT      8053
Pro Lys Thr Arg Pro Arg Lys Glu Val Lys Glu Glu Leu Ser Ala Val
    2605                2610                2615
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GAG AGG CTC ACG CAA ACA TCA GGG CAA AGC ACA CAC ACA CAC AAA GAA      8101
Glu Arg Leu Thr Gln Thr Ser Gly Gln Ser Thr His Thr His Lys Glu
2620                2625                2630                2635

CCA GCA AGC GGT GAT GAG GGC ATC AAA GTA TTG AAG CAA CGT GCA AAG      8149
Pro Ala Ser Gly Asp Glu Gly Ile Lys Val Leu Lys Gln Arg Ala Lys
                    2640                2645                2650

AAG AAA CCA AAC CCA GTA GAA GAG GAA CCC AGC AGG AGA AGG CCA AGA      8197
Lys Lys Pro Asn Pro Val Glu Glu Glu Pro Ser Arg Arg Arg Pro Arg
                2655                2660                2665

GCA CCT AAG GAA AAG GCC CAA CCC CTG GAA GAC CTG GCC GGC TTC ACA      8245
Ala Pro Lys Glu Lys Ala Gln Pro Leu Glu Asp Leu Ala Gly Phe Thr
        2670                2675                2680

GAG CTC TCT GAA ACA TCA GGT CAC ACT CAG GAA TCA CTG ACT GCT GGC      8293
Glu Leu Ser Glu Thr Ser Gly His Thr Gln Glu Ser Leu Thr Ala Gly
    2685                2690                2695

AAA GCC ACT AAA ATA CCC TGC GAA TCT CCC CCA CTA GAA GTG GTA GAC      8341
Lys Ala Thr Lys Ile Pro Cys Glu Ser Pro Pro Leu Glu Val Val Asp
2700                2705                2710                2715

ACC ACA GCA AGC ACA AAG AGG CAT CTC AGG ACA CGT GTG CAG AAG GTA      8389
Thr Thr Ala Ser Thr Lys Arg His Leu Arg Thr Arg Val Gln Lys Val
                    2720                2725                2730

CAA GTA AAA GAA GAG CCT TCA GCA GTC AAG TTC ACA CAA ACA TCA GGG      8437
Gln Val Lys Glu Glu Pro Ser Ala Val Lys Phe Thr Gln Thr Ser Gly
                2735                2740                2745

GAA ACC ACG GAT GCA GAC AAA GAA CCA GCA GGT GAA GAT AAA GGC ATC      8485
Glu Thr Thr Asp Ala Asp Lys Glu Pro Ala Gly Glu Asp Lys Gly Ile
        2750                2755                2760

AAA GCA TTG AAG GAA TCT GCA AAA CAG ACA CCG GCT CCA GCA GCA AGT      8533
Lys Ala Leu Lys Glu Ser Ala Lys Gln Thr Pro Ala Pro Ala Ala Ser
    2765                2770                2775

GTA ACT GGC AGC AGG AGA CGG CCA AGA GCA CCC AGG GAA AGT GCC CAA      8581
Val Thr Gly Ser Arg Arg Arg Pro Arg Ala Pro Arg Glu Ser Ala Gln
2780                2785                2790                2795

GCC ATA GAA GAC CTA GCT GGC TTC AAA GAC CCA GCA GCA GGT CAC ACT      8629
Ala Ile Glu Asp Leu Ala Gly Phe Lys Asp Pro Ala Ala Gly His Thr
                    2800                2805                2810

GAA GAA TCA ATG ACT GAT GAC AAA ACC ACT AAA ATA CCC TGC AAA TCA      8677
Glu Glu Ser Met Thr Asp Asp Lys Thr Thr Lys Ile Pro Cys Lys Ser
                2815                2820                2825

TCA CCA GAA CTA GAA GAC ACC GCA ACA AGC TCA AAG AGA CGG CCC AGG      8725
Ser Pro Glu Leu Glu Asp Thr Ala Thr Ser Ser Lys Arg Arg Pro Arg
        2830                2835                2840

ACA CGT GCC CAG AAA GTA GAA GTG AAG GAG GAG CTG TTA GCA GTT GGC      8773
Thr Arg Ala Gln Lys Val Glu Val Lys Glu Glu Leu Leu Ala Val Gly
    2845                2850                2855

AAG CTC ACA CAA ACC TCA GGG GAG ACC ACG CAC ACC GAC AAA GAG CCG      8821
Lys Leu Thr Gln Thr Ser Gly Glu Thr Thr His Thr Asp Lys Glu Pro
2860                2865                2870                2875
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GTA GGT GAG GGC AAA GGC ACG AAA GCA TTT AAG CAA CCT GCA AAG CGG      8869
Val Gly Glu Gly Lys Gly Thr Lys Ala Phe Lys Gln Pro Ala Lys Arg
                2880                2885                2890

AAC GTG GAC GCA GAA GAT GTA ATT GGC AGC AGG AGA CAG CCA AGA GCA      8917
Asn Val Asp Ala Glu Asp Val Ile Gly Ser Arg Arg Gln Pro Arg Ala
            2895                2900                2905

CCT AAG GAA AAG GCC CAA CCC CTG GAA GAC CTG GCC AGC TTC CAA GAG      8965
Pro Lys Glu Lys Ala Gln Pro Leu Glu Asp Leu Ala Ser Phe Gln Glu
        2910                2915                2920

CTC TCT CAA ACA CCA GGC CAC ACT GAG GAA CTG GCA AAT GGT GCT GCT      9013
Leu Ser Gln Thr Pro Gly His Thr Glu Glu Leu Ala Asn Gly Ala Ala
    2925                2930                2935

GAT AGC TTT ACA AGC GCT CCA AAG CAA ACA CCT GAC AGT GGA AAA CCT      9061
Asp Ser Phe Thr Ser Ala Pro Lys Gln Thr Pro Asp Ser Gly Lys Pro
2940                2945                2950                2955

CTA AAA ATA TCC AGA AGA GTT CTT CGG GCC CCT AAA GTA GAA CCC GTG      9109
Leu Lys Ile Ser Arg Arg Val Leu Arg Ala Pro Lys Val Glu Pro Val
                2960                2965                2970

GGA GAC GTG GTA AGC ACC AGA GAC CCT GTA AAA TCA CAA AGC AAA AGC      9157
Gly Asp Val Val Ser Thr Arg Asp Pro Val Lys Ser Gln Ser Lys Ser
            2975                2980                2985

AAC ACT TCC CTG CCC CCA CTG CCC TTC AAG AGG GGA GGT GGC AAA GAT      9205
Asn Thr Ser Leu Pro Pro Leu Pro Phe Lys Arg Gly Gly Gly Lys Asp
        2990                2995                3000

GGA AGC GTC ACG GGA ACC AAG AGG CTG CGC TGC ATG CCA GCA CCA GAG      9253
Gly Ser Val Thr Gly Thr Lys Arg Leu Arg Cys Met Pro Ala Pro Glu
    3005                3010                3015

GAA ATT GTG GAG GAG CTG CCA GCC AGC AAG AAG CAG AGG GTT GCT CCC      9301
Glu Ile Val Glu Glu Leu Pro Ala Ser Lys Lys Gln Arg Val Ala Pro
3020                3025                3030                3035

AGG GCA AGA GGC AAA TCA TCC GAA CCC GTG GTC ATC ATG AAG AGA AGT      9349
Arg Ala Arg Gly Lys Ser Ser Glu Pro Val Val Ile Met Lys Arg Ser
                3040                3045                3050

TTG AGG ACT TCT GCA AAA AGA ATT GAA CCT GCG GAA GAG CTG AAC AGC      9397
Leu Arg Thr Ser Ala Lys Arg Ile Glu Pro Ala Glu Glu Leu Asn Ser
            3055                3060                3065

AAC GAC ATG AAA ACC AAC AAA GAG GAA CAC AAA TTA CAA GAC TCG GTC      9445
Asn Asp Met Lys Thr Asn Lys Glu Glu His Lys Leu Gln Asp Ser Val
        3070                3075                3080

CCT GAA AAT AAG GGA ATA TCC CTG CGC TCC AGA CGC CAA GAT AAG ACT      9493
Pro Glu Asn Lys Gly Ile Ser Leu Arg Ser Arg Arg Gln Asp Lys Thr
    3085                3090                3095

GAG GCA GAA CAG CAA ATA ACT GAG GTC TTT GTA TTA GCA GAA AGA ATA      9541
Glu Ala Glu Gln Gln Ile Thr Glu Val Phe Val Leu Ala Glu Arg Ile
3100                3105                3110                3115

GAA ATA AAC AGA AAT GAA AAG AAG CCC ATG AAG ACC TCC CCA GAG ATG      9589
Glu Ile Asn Arg Asn Glu Lys Lys Pro Met Lys Thr Ser Pro Glu Met
                3120                3125                3130
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GAC ATT CAG AAT CCA GAT GAT GGA GCC CGG AAA CCC ATA CCT AGA GAC      9637
Asp Ile Gln Asn Pro Asp Asp Gly Ala Arg Lys Pro Ile Pro Arg Asp
          3135                3140                3145

AAA GTC ACT GAG AAC AAA AGG TGC TTG AGG TCT GCT AGA CAG AAT GAG      9685
Lys Val Thr Glu Asn Lys Arg Cys Leu Arg Ser Ala Arg Gln Asn Glu
     3150                3155                3160

AGC TCC CAG CCT AAG GTG GCA GAG GAG AGC GGA GGG CAG AAG AGT GCG      9733
Ser Ser Gln Pro Lys Val Ala Glu Glu Ser Gly Gly Gln Lys Ser Ala
3165                3170                3175

AAG GTT CTC ATG CAG AAT CAG AAA GGG AAA GGA GAA GCA GGA AAT TCA      9781
Lys Val Leu Met Gln Asn Gln Lys Gly Lys Gly Glu Ala Gly Asn Ser
3180                3185                3190                3195

GAC TCC ATG TGC CTG AGA TCA AGA AAG ACA AAA AGC CAG CCT GCA GCA      9829
Asp Ser Met Cys Leu Arg Ser Arg Lys Thr Lys Ser Gln Pro Ala Ala
               3200                3205                3210

AGC ACT TTG GAG AGC AAA TCT GTG CAG AGA GTA ACG CGG AGT GTC AAG      9877
Ser Thr Leu Glu Ser Lys Ser Val Gln Arg Val Thr Arg Ser Val Lys
          3215                3220                3225

AGG TGT GCA GAA AAT CCA AAG AAG GCT GAG GAC AAT GTG TGT GTC AAG      9925
Arg Cys Ala Glu Asn Pro Lys Lys Ala Glu Asp Asn Val Cys Val Lys
     3230                3235                3240

AAA ATA ACA ACC AGA AGT CAT AGG GAC AGT GAA GAT ATT TGACAGAAAA       9974
Lys Ile Thr Thr Arg Ser His Arg Asp Ser Glu Asp Ile
3245                3250                3255

ATCGAACTGG GAAAAATATA ATAAAGTTAG TTTTGTGATA AGTTCTAGTG CAGTTTTTGT   10034

CATAAATTAC AAGTGAATTC TGTAAGTAAG GCTGTCAGTC TGCTTAAGGG AAGAAAACTT   10094

TGGATTTGCT GGGTCTGAAT CGGCTTCATA AACTCCACTG GGAGCACTGC TGGGCTCCTG   10154

GACTGAGAAT AGTTGAACAC CGGGGGCTTT GTGAAGGAGT CTGGGCCAAG GTTTGCCCTC   10214

AGCTTTGCAG AATGAAGCCT TGAGGTCTGT CACCACCCAC AGCCACCCTA CAGCAGCCTT   10274

AACTGTGACA CTTGCCACAC TGTGTCGTCG TTTGTTTGCC TATGTTCTCC AGGGCACGGT   10334

GGCAGGAACA ACTATCCTCG TCTGTCCCAA CACTGAGCAG GCACTCGGTA AACACGAATG   10394

AATGGATAAG CGCACGGATG AATGGAGCTT ACAAGATCTG TCTTTCCAAT GGCCGGGGGC   10454

ATTTGGTCCC CAAATTAAGG CTATTGGACA TCTGCACAGG ACAGTCCTAT TTTTGATGTC   10514

CTTTCCTTTC TGAAAATAAA GTTTTGTGCT TTGGAGAATG ACTCGTGAGC ACATCTTTAG   10574

GGACCAAGAG TGACTTTCTG TAAGGAGTGA CTCGTGGCTT GCCTTGGTCT CTTGGGAATA   10634

CTTTTCTAAC TAGGGTTGCT CTCACCTGAG ACATTCTCCA CCCGCGGAAT CTCAGGGTCC   10694

CAGGCTGTGG GCCATCACGA CCTCAAACTG GCTCCTAATC TCCAGCTTTC CTGTCATTGA   10754

AAGCTTCGGA AGTTTACTGG CTCTGCTCCC GCCTGTTTTC TTTCTGACTC TATCTGGCAG   10814

CCCGATGCCA CCCAGTACAG GAAGTGACAC CAGTACTCTG TAAAGCATCA TCATCCTTGG   10874

AGAGACTGAG CACTCAGCAC CTTCAGCCAC GATTTCAGGA TCGCTTCCTT GTGAGCCGCT   10934
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GCCTCCGAAA TCTCCTTTGA AGCCCAGACA TCTTTCTCCA GCTTCAGACT TGTAGATATA 10994

ACTCGTTCAT CTTCATTTAC TTTCCACTTT GCCCCCTGTC CTCTCTGTGT TCCCCAAATC 11054

AGAGAATAGC CCGCCATCCC CCAGATCACC TGTCTGGATT CCTCCCCATT CACCCACCTT 11114

GCCAGGTGCA GGTGAGGATG GTGCACCAGA CAGGGTAGCT GTCCCCCAAA ATGTGCCCTG 11174

TGCGGGCAGT GCCCTGTCTC CACGTTTGTT TCCCCAGTGT CTGGCGGGGA GCCAGGTGAC 11234

ATCATAAATA CTTGCTGAAT GAATGCAGAA ATCAGCGGTA CTGACTTGTA CTATATTGGC 11294

TGCCATGATA GGGTTCTCAC AGCGTCATCC ATGATCGTAA GGGAGAATGA CATTCTGCTT 11354

GAGGGAGGGA ATAGAAAGGG GCAGGGAGGG GACATCTGAG GGCTTCACAG GGCTGCAAAG 11414

GGTACAGGGA TTGCACCAGG GCAGAACAGG GGAGGGTGTT CAAGGAAGAG TGGCTCTTAG 11474

CAGAGGCACT TTGGAAGGTG TGAGGCATAA ATGCTTCCTT CTACGTAGGC CAACCTCAAA 11534

ACTTTCAGTA GGAATGTTGC TATGATCAAG TTGTTCTAAC ACTTTAGACT TAGTAGTAAT 11594

TATGAACCTC ACATAGAAAA ATTTCATCCA GCCATATGCC TGTGGAGTGG AATATTCTGT 11654

TTAGTAGAAA AATCCTTTAG AGTTCAGCTC TAACCAGAAA TCTTGCTGAA GTATGTCAGC 11714

ACCTTTTCTC ACCCTGGTAA GTACAGTATT TCAAGAGCAC GCTAAGGGTG GTTTTCATTT 11774

TACAGGGCTG TTGATGATGG GTTAAAAATG TTCATTTAAG GGCTACCCCC GTGTTTAATA 11834

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ACTGCCCATT CCCCTAGGCT GACTGGATTT GAGAACAAAT ACCCACCCAT TTCCACCATG 11954

GTATGGTAAC TTCTCTGAGC TTCAGTTTCC AAGTGAATTT CCATGTAATA GGACATTCCC 12014

ATTAAATACA AGCTGTTTTT ACTTTTTCGC CTCCCAGGGC CTGTGCGATC TGGTCCCCCA 12074

GCCTCTCTTG GGCTTTCTTA CACTAACTCT GTACCTACCA TCTCCTGCCT CCCTTAGGCA 12134

GGCACCTCCA ACCACCACAC ACTCCCTGCT GTTTTCCCTG CCTGGAACTT TCCCACCAGC 12194

CCCACCAAGA TCATTTCATC CAGTCCTGAG CTCAGCTTAA GGGAGGCTTC TTGCCTGTGG 12254

GTTCCCTCAC CCCCATGCCT GTCCTCCAGG CTGGGGCAGG TTCTTAGTTT GCCTGGAATT 12314

GTTCTGTACC TCTTTGTAGC ACGTAGTGTT GTGAAACTAA GCCACTAATT GAGTTTCTGG 12374

CTCCCCTCCT GGGGTTGTAA GTTTTGTTCA TTCATGAGGG CCGACTGTAT TTCCTGGTTA 12434

CTGTATCCCA GTGACCAGCC ACAGGAGATG TCCAATAAAG TATGTGATGA AATGGTCTT 12493

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3256 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein
(xi) SEQUENCE DISCRIPTION: SEQ ID NO: 2:

Met Trp Pro Thr Arg Arg Leu Val Thr Ile Lys Arg Ser Gly Val Asp
1 5 10 15

Gly Pro His Phe Pro Leu Ser Leu Ser Thr Cys Leu Phe Gly Arg Gly
20 25 30

Ile Glu Cys Asp Ile Arg Ile Gln Leu Pro Val Val Ser Lys Gln His
35 40 45

Cys Lys Val Glu Ile His Glu Gln Glu Ala Ile Leu His Asn Phe Ser
50 55 60

Ser Thr Asn Pro Thr Gln Val Asn Gly Ser Val Ile Asp Glu Pro Val
65 70 75 80

Arg Leu Lys His Gly Asp Val Ile Thr Ile Ile Asp Arg Ser Phe Arg
85 90 95

Tyr Glu Asn Glu Ser Leu Gln Asn Gly Arg Lys Ser Thr Glu Phe Pro
100 105 110

Arg Lys Ile Arg Glu Gln Glu Pro Ala Arg Arg Val Ser Arg Ser Ser
115 120 125

Phe Ser Ser Asp Pro Asp Glu Lys Ala Gln Asp Ser Lys Ala Tyr Ser
130 135 140

Lys Ile Thr Glu Gly Lys Val Ser Gly Asn Pro Gln Val His Ile Lys
145 150 155 160

Asn Val Lys Glu Asp Ser Thr Ala Asp Asp Ser Lys Asp Ser Val Ala
165 170 175

Gln Gly Thr Thr Asn Val His Ser Ser Glu His Ala Gly Arg Asn Gly
180 185 190

Arg Asn Ala Ala Asp Pro Ile Ser Gly Asp Phe Lys Glu Ile Ser Ser
195 200 205

Val Lys Leu Val Ser Arg Tyr Gly Glu Leu Lys Ser Val Pro Thr Thr
210 215 220

Gln Cys Leu Asp Asn Ser Lys Lys Asn Glu Ser Pro Phe Trp Lys Leu
225 230 235 240

Tyr Glu Ser Val Lys Lys Glu Leu Asp Val Lys Ser Gln Lys Glu Asn
245 250 255

Val Leu Gln Tyr Cys Arg Lys Ser Gly Leu Gln Thr Asp Tyr Ala Thr
260 265 270

Glu Lys Glu Ser Ala Asp Gly Leu Gln Gly Glu Thr Gln Leu Leu Val
275 280 285

Ser Arg Lys Ser Arg Pro Lys Ser Gly Gly Ser Gly His Ala Val Ala
290 295 300

Glu Pro Ala Ser Pro Glu Gln Glu Leu Asp Gln Asn Lys Gly Lys Gly
305 310 315 320

Arg Asp Val Glu Ser Val Gln Thr Pro Ser Lys Ala Val Gly Ala Ser
325 330 335

Phe Pro Leu Tyr Glu Pro Ala Lys Met Lys Thr Pro Val Gln Tyr Ser
340 345 350

Gln Gln Gln Asn Ser Pro Gln Lys His Lys Asn Lys Asp Leu Tyr Thr
355 360 365

Thr Gly Arg Arg Glu Ser Val Asn Leu Gly Lys Ser Glu Gly Phe Lys
370 375 380

Ala Gly Asp Lys Thr Leu Thr Pro Arg Lys Leu Ser Thr Arg Asn Arg
385 390 395 400

Thr Pro Ala Lys Val Glu Asp Ala Ala Asp Ser Ala Thr Lys Pro Glu
405 410 415

Asn Leu Ser Ser Lys Thr Arg Gly Ser Ile Pro Thr Asp Val Glu Val
420 425 430

Leu Pro Thr Glu Thr Glu Ile His Asn Glu Pro Phe Leu Thr Leu Trp
435 440 445

Leu Thr Gln Val Glu Arg Lys Ile Gln Lys Asp Ser Leu Ser Lys Pro
450 455 460

Glu Lys Leu Gly Thr Thr Ala Gly Gln Met Cys Ser Gly Leu Pro Gly
465 470 475 480

Leu Ser Ser Val Asp Ile Asn Asn Phe Gly Asp Ser Ile Asn Glu Ser
485 490 495

Glu Gly Ile Pro Leu Lys Arg Arg Arg Val Ser Phe Gly Gly His Leu
500 505 510

Arg Pro Glu Leu Phe Asp Glu Asn Leu Pro Pro Asn Thr Pro Leu Lys
515 520 525

Arg Gly Glu Ala Pro Thr Lys Arg Lys Ser Leu Val Met His Thr Pro
530 535 540

Pro Val Leu Lys Lys Ile Ile Lys Glu Gln Pro Gln Pro Ser Gly Lys
545 550 555 560

Gln Glu Ser Gly Ser Glu Ile His Val Glu Val Lys Ala Gln Ser Leu
565 570 575

Val Ile Ser Pro Pro Ala Pro Ser Pro Arg Lys Thr Pro Val Ala Ser
580 585 590

Asp Gln Arg Arg Arg Ser Cys Lys Thr Ala Pro Ala Ser Ser Ser Lys
595 600 605

Ser Gln Thr Glu Val Pro Lys Arg Gly Gly Glu Arg Val Ala Thr Cys
610 615 620

Leu Gln Lys Arg Val Ser Ile Ser Arg Ser Gln His Asp Ile Leu Gln
625 630 635 640

Met Ile Cys Ser Lys Arg Arg Ser Gly Ala Ser Glu Ala Asn Leu Ile
645 650 655

Val Ala Lys Ser Trp Ala Asp Val Val Lys Leu Gly Ala Lys Gln Thr
660 665 670

Gln Thr Lys Val Ile Lys His Gly Pro Gln Arg Ser Met Asn Lys Arg
675 680 685

Gln Arg Arg Pro Ala Thr Pro Lys Lys Pro Val Gly Glu Val His Ser
690 695 700

Gln Phe Ser Thr Gly His Ala Asn Ser Pro Cys Thr Ile Ile Ile Gly
705 710 715 720

Lys Ala His Thr Glu Lys Val His Val Pro Ala Arg Pro Tyr Arg Val
725 730 735

Leu Asn Asn Phe Ile Ser Asn Gln Lys Met Asp Phe Lys Glu Asp Leu
740 745 750

Ser Gly Ile Ala Glu Met Phe Lys Thr Pro Val Lys Glu Gln Pro Gln
755 760 765

Leu Thr Ser Thr Cys His Ile Ala Ile Ser Asn Ser Glu Asn Leu Leu
770 775 780

Gly Lys Gln Phe Gln Gly Thr Asp Ser Gly Glu Glu Pro Leu Leu Pro
785 790 795 800

Thr Ser Glu Ser Phe Gly Gly Asn Val Phe Phe Ser Ala Gln Asn Ala
805 810 815

Ala Lys Gln Pro Ser Asp Lys Cys Ser Ala Ser Pro Pro Leu Arg Arg
820 825 830

Gln Cys Ile Arg Glu Asn Gly Asn Val Ala Lys Thr Pro Arg Asn Thr
835 840 845

Tyr Lys Met Thr Ser Leu Glu Thr Lys Thr Ser Asp Thr Glu Thr Glu
850 855 860

Pro Ser Lys Thr Val Ser Thr Val Asn Arg Ser Gly Arg Ser Thr Glu
865 870 875 880

Phe Arg Asn Ile Gln Lys Leu Pro Val Glu Ser Lys Ser Glu Glu Thr
885 890 895

Asn Thr Glu Ile Val Glu Cys Ile Leu Lys Arg Gly Gln Lys Ala Thr
900 905 910

Leu Leu Gln Gln Arg Arg Glu Gly Glu Met Lys Glu Ile Glu Arg Pro
915 920 925

Phe Glu Thr Tyr Lys Glu Asn Ile Glu Leu Lys Glu Asn Asp Glu Lys
930 935 940

Met Lys Ala Met Lys Arg Ser Arg Thr Trp Gly Gln Lys Cys Ala Pro
945 950 955 960

Met Ser Asp Leu Thr Asp Leu Lys Ser Leu Pro Asp Thr Glu Leu Met
965 970 975

Lys Asp Thr Ala Arg Gly Gln Asn Leu Leu Gln Thr Gln Asp His Ala
980 985 990

Lys Ala Pro Lys Ser Glu Lys Gly Lys Ile Thr Lys Met Pro Cys Gln
995 1000 1005

Ser Leu Gln Pro Glu Pro Ile Asn Thr Pro Thr His Thr Lys Gln Gln
1010 1015 1020

Leu Lys Ala Ser Leu Gly Lys Val Gly Val Lys Glu Glu Leu Leu Ala
1025 1030 1035 1040

Val Gly Lys Phe Thr Arg Thr Ser Gly Glu Thr Thr His Thr His Arg
1045 1050 1055

Glu Pro Ala Gly Asp Gly Lys Ser Ile Arg Thr Phe Lys Glu Ser Pro
1060 1065 1070

Lys Gln Ile Leu Asp Pro Ala Ala Arg Val Thr Gly Met Lys Lys Trp
1075 1080 1085

Pro Arg Thr Pro Lys Glu Glu Ala Gln Ser Leu Glu Asp Leu Ala Gly
1090 1095 1100

Phe Lys Glu Leu Phe Gln Thr Pro Gly Pro Ser Glu Glu Ser Met Thr
1105 1110 1115 1120

Asp Glu Lys Thr Thr Lys Ile Ala Cys Lys Ser Pro Pro Pro Glu Ser
1125 1130 1135

Val Asp Thr Pro Thr Ser Thr Lys Gln Trp Pro Lys Arg Ser Leu Arg
1140 1145 1150

Lys Ala Asp Val Glu Glu Glu Phe Leu Ala Leu Arg Lys Leu Thr Pro
1155 1160 1165

Ser Ala Gly Lys Ala Met Leu Thr Pro Lys Pro Ala Gly Gly Asp Glu
1170 1175 1180

Lys Asp Ile Lys Ala Phe Met Gly Thr Pro Val Gln Lys Leu Asp Leu
1185 1190 1195 1200

Ala Gly Thr Leu Pro Gly Ser Lys Arg Gln Leu Gln Thr Pro Lys Glu
1205 1210 1215

Lys Ala Gln Ala Leu Glu Asp Leu Ala Gly Phe Lys Glu Leu Phe Gln
1220 1225 1230

Thr Pro Gly His Thr Glu Glu Leu Val Ala Ala Gly Lys Thr Thr Lys
1235 1240 1245

Ile Pro Cys Asp Ser Pro Gln Ser Asp Pro Val Asp Thr Pro Thr Ser
1250 1255 1260

Thr Lys Gln Arg Pro Lys Arg Ser Ile Arg Lys Ala Asp Val Glu Gly
1265 1270 1275 1280

Glu Leu Leu Ala Cys Arg Asn Leu Met Pro Ser Ala Gly Lys Ala Met
1285 1290 1295

His Thr Pro Lys Pro Ser Val Gly Glu Glu Lys Asp Ile Ile Ile Phe
1300 1305 1310

Val Gly Thr Pro Val Gln Lys Leu Asp Leu Thr Glu Asn Leu Thr Gly
1315 1320 1325

Ser Lys Arg Arg Pro Gln Thr Pro Lys Glu Glu Ala Gln Ala Leu Glu
1330 1335 1340

Asp Leu Thr Gly Phe Lys Glu Leu Phe Gln Thr Pro Gly His Thr Glu
1345 1350 1355 1360

Glu Ala Val Ala Ala Gly Lys Thr Thr Lys Met Pro Cys Glu Ser Ser
1365 1370 1375

Pro Pro Glu Ser Ala Asp Thr Pro Thr Ser Thr Arg Arg Gln Pro Lys
1380 1385 1390

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Lys Leu Thr Gln Thr Ser Gly Glu Thr Thr His Thr Asp Lys Val Pro
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Gly Gly Glu Asp Lys Ser Ile Asn Ala Phe Arg Glu Thr Ala Lys Gln
1425 1430 1435 1440

Lys Leu Asp Pro Ala Ala Ser Val Thr Gly Ser Lys Arg His Pro Lys
1445 1450 1455

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1460 1465 1470

Leu Phe Gln Thr Pro Val Cys Thr Asp Lys Pro Thr Thr His Glu Lys
1475 1480 1485

Thr Thr Lys Ile Ala Cys Arg Ser Gln Pro Asp Pro Val Asp Thr Pro
1490 1495 1500

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1525 1530 1535

Ala Met His Thr Pro Lys Pro Ala Val Ser Gly Glu Lys Asn Ile Tyr
1540 1545 1550

Ala Phe Met Gly Thr Pro Val Gln Lys Leu Asp Leu Thr Glu Asn Leu
1555 1560 1565

Thr Gly Ser Lys Arg Arg Leu Gln Thr Pro Lys Glu Lys Ala Gln Ala
1570 1575 1580

Leu Glu Asp Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr Arg Gly His
1585 1590 1595 1600

Thr Glu Glu Ser Met Thr Asn Asp Lys Thr Ala Lys Val Ala Cys Lys
1605 1610 1615

Ser Ser Gln Pro Asp Leu Asp Lys Asn Pro Ala Ser Ser Lys Arg Arg
1620 1625 1630

Leu Lys Thr Ser Leu Gly Lys Val Gly Val Lys Glu Glu Leu Leu Ala
1635 1640 1645

Val Gly Lys Leu Thr Gln Thr Ser Gly Glu Thr Thr His Thr His Thr
1650 1655 1660

Glu Pro Thr Gly Asp Gly Lys Ser Met Lys Ala Phe Met Glu Ser Pro
1665 1670 1675 1680

Lys Gln Ile Leu Asp Ser Ala Ala Ser Leu Thr Gly Ser Lys Arg Gln
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Phe Ile Glu Leu Phe Gln Thr Pro Ser His Thr Lys Glu Ser Met Thr
1715 1720 1725

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            1780                1785                1790

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Pro Gly Asn Leu Pro Gly Ser Asn Arg Arg Leu Gln Thr Arg Lys Glu
    1810                1815                1820

Lys Ala Gln Ala Leu Glu Glu Leu Thr Gly Phe Arg Glu Leu Phe Gln
1825                1830                1835                1840

Thr Pro Cys Thr Asp Asn Pro Thr Ala Asp Glu Lys Thr Thr Lys Lys
                1845                1850                1855

Ile Leu Cys Lys Ser Pro Gln Ser Asp Pro Ala Asp Thr Pro Thr Asn
            1860                1865                1870

Thr Lys Gln Arg Pro Lys Arg Ser Leu Lys Lys Ala Asp Val Glu Glu
        1875                1880                1885

Glu Phe Leu Ala Phe Arg Lys Leu Thr Pro Ser Ala Gly Lys Ala Met
    1890                1895                1900

His Thr Pro Lys Ala Ala Val Gly Glu Glu Lys Asp Ile Asn Thr Phe
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Val Gly Thr Pro Val Glu Lys Leu Asp Leu Leu Gly Asn Leu Pro Gly
                1925                1930                1935

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            1940                1945                1950

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        1955                1960                1965

Glu Ser Met Thr Asp Asp Lys Ile Thr Glu Val Ser Cys Lys Ser Pro
    1970                1975                1980

Gln Pro Asp Pro Val Lys Thr Pro Thr Ser Ser Lys Gln Arg Leu Lys
1985                1990                1995                2000

Ile Ser Leu Gly Lys Val Gly Val Lys Glu Glu Val Leu Pro Val Gly
                2005                2010                2015

Lys Leu Thr Gln Thr Ser Gly Lys Thr Thr Gln Thr His Arg Glu Thr
            2020                2025                2030

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Thr Pro Lys Glu Glu Ala Gln Ser Leu Glu Asp Leu Ala Gly Phe Lys
2065                2070                2075                2080
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2115 2120 2125

Asp Ile Val Glu Glu Leu Ser Ala Leu Lys Gln Leu Thr Gln Thr Thr
2130 2135 2140

His Thr Asp Lys Val Pro Gly Asp Glu Asp Lys Gly Ile Asn Val Phe
2145 2150 2155 2160

Arg Glu Thr Ala Lys Gln Lys Leu Asp Pro Ala Ala Ser Val Thr Gly
2165 2170 2175

Ser Lys Arg Gln Pro Arg Thr Pro Lys Gly Lys Ala Gln Pro Leu Glu
2180 2185 2190

Asp Leu Ala Gly Leu Lys Glu Leu Phe Gln Thr Pro Val Cys Thr Asp
2195 2200 2205

Lys Pro Thr Thr His Glu Lys Thr Thr Lys Ile Ala Cys Arg Ser Pro
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Gln Pro Asp Pro Val Gly Thr Pro Thr Ile Phe Lys Pro Gln Ser Lys
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Lys Arg Thr Pro Ser Val Gly Lys Ala Met Asp Thr Pro Lys Pro Ala
2260 2265 2270

Gly Gly Asp Glu Lys Asp Met Lys Ala Phe Met Gly Thr Pro Val Gln
2275 2280 2285

Lys Leu Asp Leu Pro Gly Asn Leu Pro Gly Ser Lys Arg Trp Pro Gln
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2385 2390 2395 2400

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2405 2410 2415

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2420 2425 2430

Ala Leu Glu Asp Leu Val Gly Phe Lys Glu Leu Phe Gln Thr Pro Gly
2435 2440 2445

His Thr Glu Glu Ser Met Thr Asp Asp Lys Ile Thr Glu Val Ser Cys
2450 2455 2460

Lys Ser Pro Gln Pro Glu Ser Phe Lys Thr Ser Arg Ser Ser Lys Gln
2465 2470 2475 2480

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2485 2490 2495

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2885 2890 2895

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3205 3210 3215

Lys Ser Val Gln Arg Val Thr Arg Ser Val Lys Arg Cys Ala Glu Asn
3220 3225 3230

Pro Lys Lys Ala Glu Asp Asn Val Cys Val Lys Lys Ile Thr Thr Arg
3235 3240 3245

Ser His Arg Asp Ser Glu Asp Ile
3250 3255

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS
(A) LENGTH: 23 base pairs
(B) TYPE: Nucleotid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) description: /desc = "synthetic oligonucleotide"

(xi) SEQUENCE DISCRIPTION: SEQ ID NO: 3:

ACCAGGCGTC TCGTGGGCCA CAT 23

Patent claims

1. Use of an oligoribo- or oligodeoxyribonucleotide which is capable of hybridizing with the mRNA which codes for the protein Ki-67, or of a physiologically acceptable salt thereof, for the preparation of a medicament for destroying proliferating cells.

2. Use according to claim 1, **characterized in that** the nucleotide sequence of the oligoribo- or oligodeoxyribonucleotide is complementary to SEQ ID NO 1.

3. Use according to claim 2, **characterized in that** the nucleotide sequence of the oligoribo- or oligodeoxyribonucleotide is complementary to the section from position 197 to 9962 of SEQ ID NO 1.

4. Use according to anyone of claims 1 to 3, **characterized in that** the oligoribo- or oligodeoxyribonucleotide contains 12 to 66 nucleotides.

5. Use according to anyone of claims 1 to 4, **characterized in that** the oligoribo- or oligodeoxyribonucleotide contains 17 to 46 nucleotides.

6. Use according to anyone of claims 1 to 5, **characterized in that** the oligoribo- or oligodeoxyribonucleotide has the sequence (5'-ACC AGG CGT CTC GTG GGC CAC AT).

7. Use according to anyone of claims 1 to 6, **characterized in that** one or more phosphate groups of the oligoribo- or oligodeoxyribonucleotide are replaced by phosphothioate, methylphosphonate, phosphoramidate, methylene(methylimino) and/or guanidine group(s).

8. Use according to anyone of claims 1 to 7, **characterized in that** the oligoribo- or oligodeoxyribonucleotide has a terminal 3'-3' and/or 5'-5' internucleotide linkage.

9. Medicament, **characterized by** a content of an oligoribo- and/or oligodeoxyribonucleotide which is capable of hybridizing with the mRNA which codes for the cell cycle-associated protein Ki-67, or of a physiologically acceptable salt thereof, in addition to conventional carrier substances, auxiliaries and/or additives, wherein the amount of oligonucleotide is adjusted such that an administration of 0.001 to 100 mg/kg of body weight is achieved.

10. Use according to anyone of claims 1 to 8 for treatment of tumours, autoimmune diseases, cicatrization, inflammations, allergies, rheumatic diseases and rejection reactions following transplantations.

11. Process for the preparation of a medicament for destroying proliferating cells, **characterized by** the use of oligoribo- or oligodeoxyribonucleotides which are capable of hybridizing with the mRNA which codes for the protein Ki-67, or of a physiologically acceptable salt thereof.

12. Process according to claim 11 for the preparation of a medicament for treatment of tumours, autoimmune diseases, cicatrization, inflammations, allergies, rheumatic diseases or rejection reactions following transplantations.

13. Process according to claim 11 or 12, comprising combining of an oligoribo- or oligodeoxyribonucleotide which is capable of hybridizing with the mRNA which codes for the protein Ki-67 with conventional carrier substances, auxiliaries and/or additives.

14. Oligoribo- or oligodeoxyribonucleotide, **characterized in that** it is capable of hybridizing with the mRNA which codes for the protein Ki-67, and that it contains 22 to 46 nucleotides, or a physiologically acceptable salt thereof.

15. Oligoribo- or oligodeoxyribonucleotide according to claim 14, **characterized in that** it contains the sequence (5' -ACC AGG TGA GCC GAG GAC GCC AT).

Abstract

The invention relates to oligoribo- and oligodeoxyribonucleotides which are suitable for treating pathological conditions accompanied by increased cell proliferation. The oligoribo- and oligodeoxyribonucleotides are characterized in that they are able to hybridise with the mRNA which codes for the cell cycle-associated protein Ki-67.

Figure 1

Complete nucleotide sequence of the cDNA of the protein Ki-67 and the protein amino acid sequence derived therefrom.

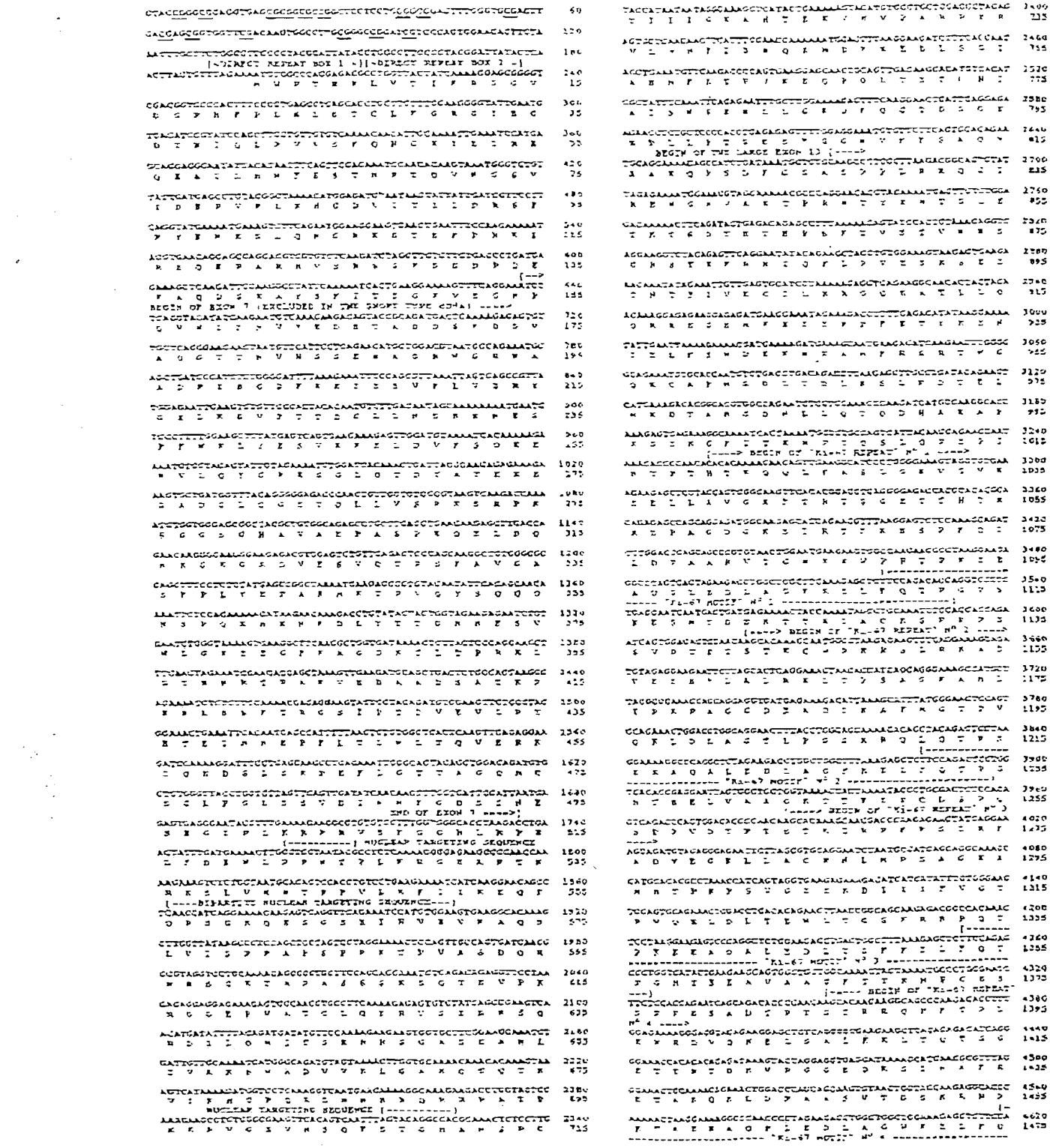


Figure 1
(continued)

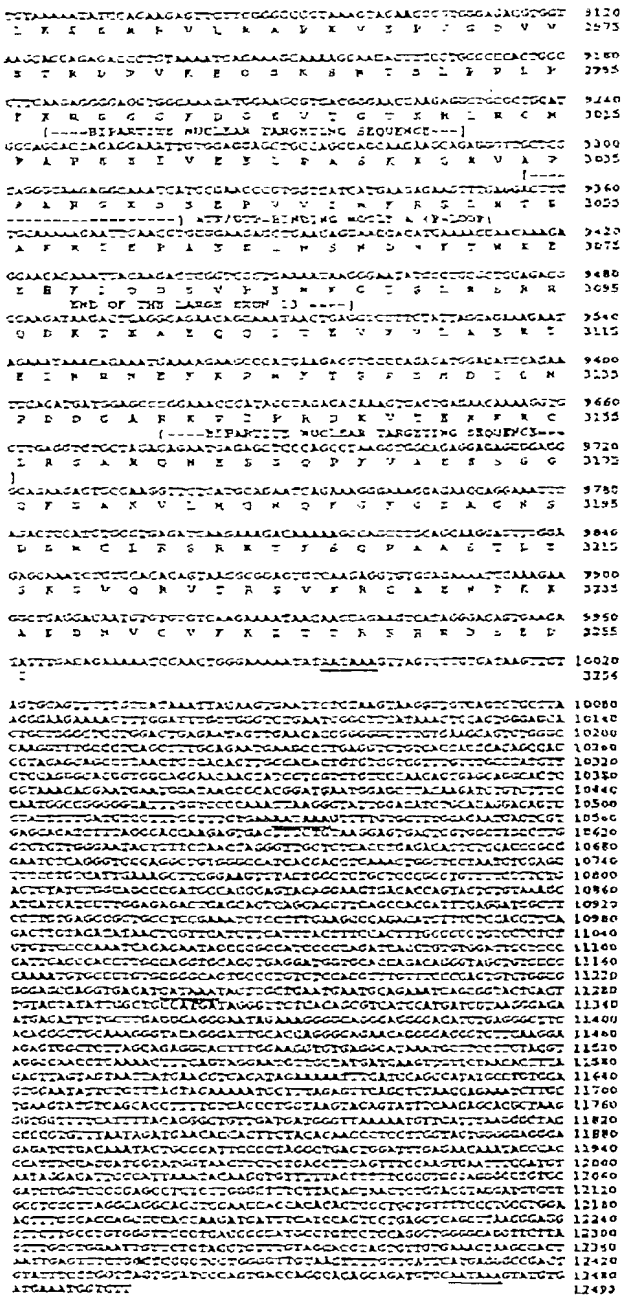


Figure 2

Structure of sugar- and phosphate-modified oligonucleotides

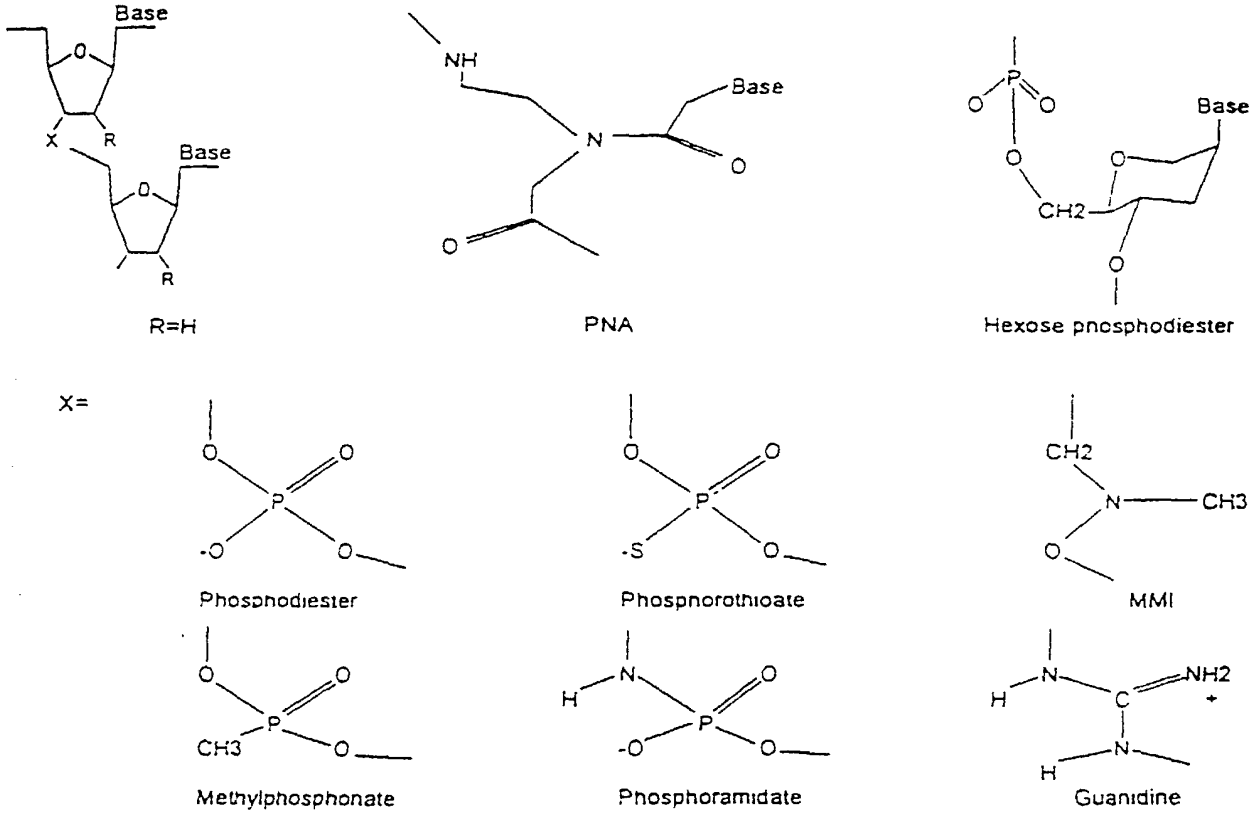


Figure 3

Influence of oligonucleotides on RT4 cells.

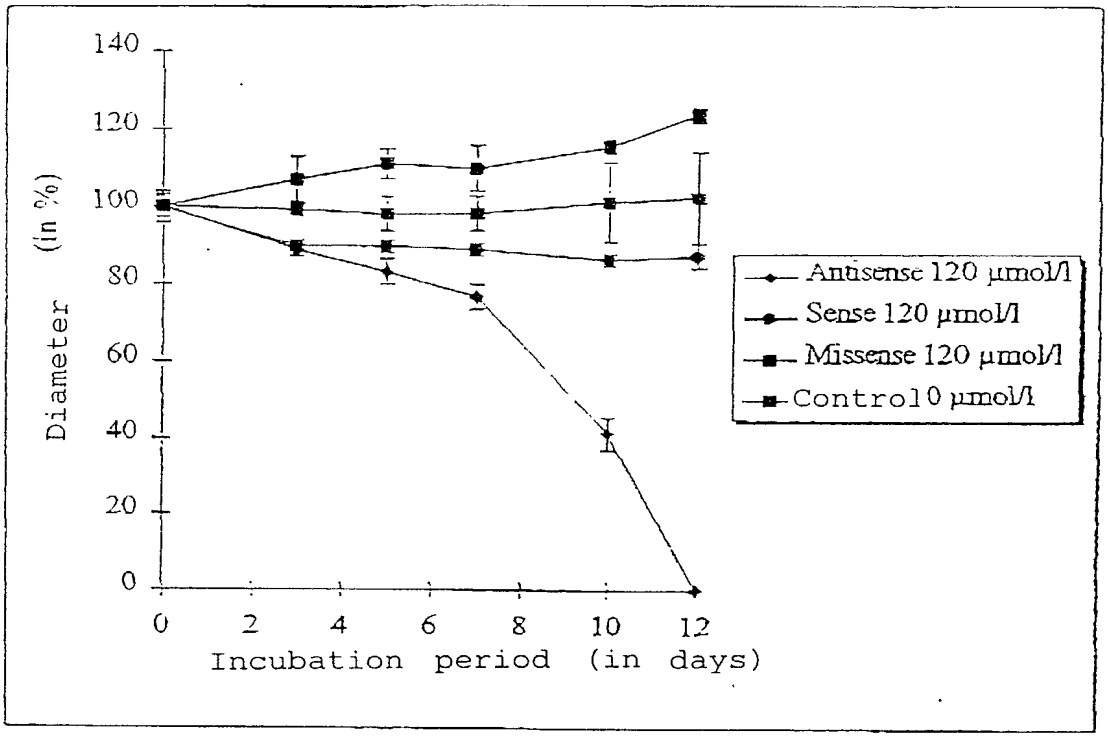


Figure 4

Influence of the solvent on RT4 cells
(negative control)

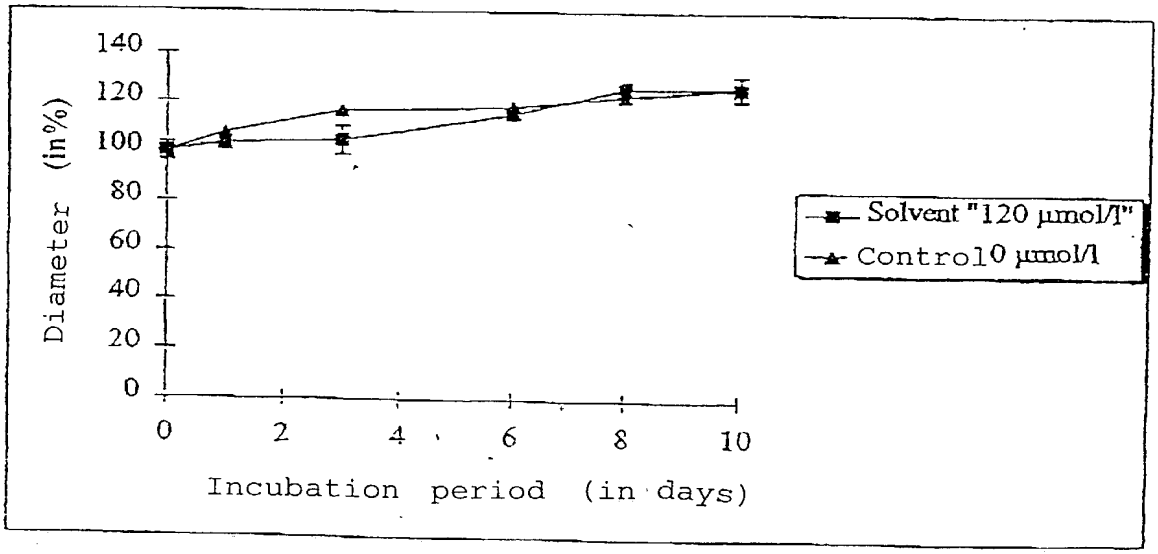


Figure 5

Influence of oligonucleotides on RT4 cells by microinjection

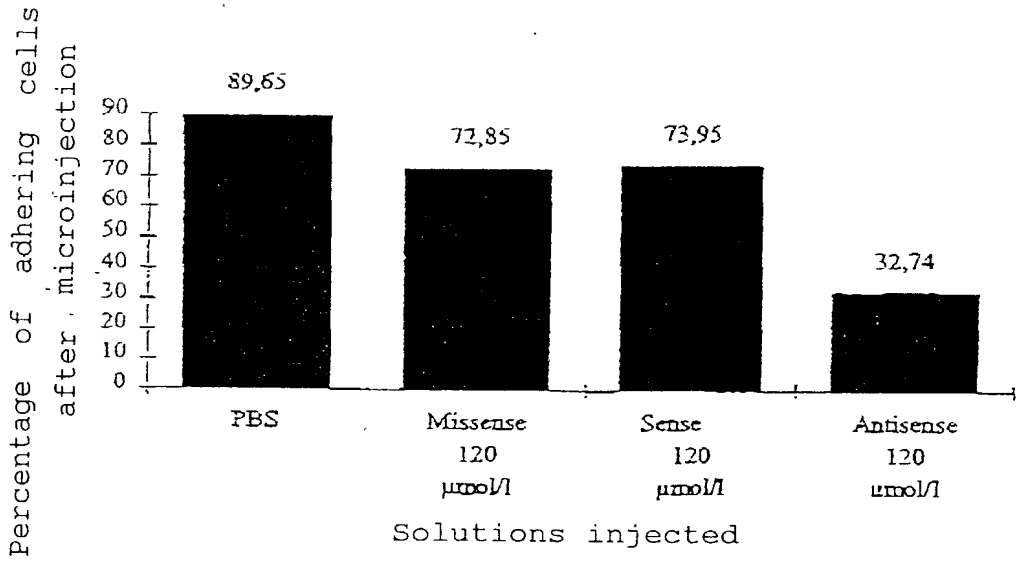
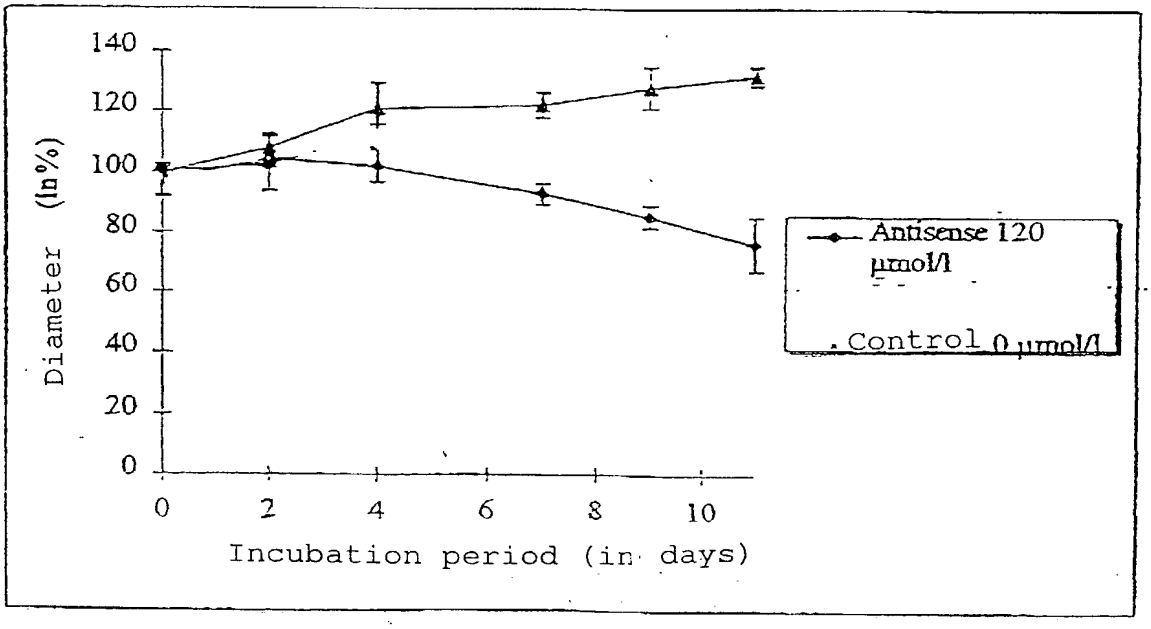


Figure 6

Influence of oligonucleotides on J82 cells



DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

[ ] Declaration Submitted with Initial Filing or [X] Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e) required)

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED "ANTISENSE OLIGONUCLEOTIDES FOR TREATING PROLIFERATING CELLS", the specification of which was filed on November 21, 2000 as Attorney Docket No. 661-50303, which is a U.S. National Phase application of PCT International Application No. PCT/EP99/03451.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 including for continuation-in-part application, material information which becomes available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a) -(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international Application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)			Priority Claimed	Certified Copy Attached?
Number	Country	Foreign Filing Date (MM/DD/YYYY)		Yes No
PCT/EP99/03451		May 20, 1999	Yes	
198 22 954.2	DE	May 22, 1998	Yes	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the registered practitioners represented by Customer No.: 20736 to prosecute this application and transact all business in the U.S. Patent and Trademark Office in connection therewith. Direct all correspondence to Farkas & Manelli, PLLC at Customer No.: 20736.

1. INVENTOR'S SIGNATURE: H.D. Flad Date 20/02/01
   Inventor's Name (typed) Hans-Dieter (First) DEX (Middle Initial) Flad (Family Name) Germany (Country of Citizenship)
   Residence (City) Borstel (State) Germany
   Post Office Address (Include Zip Code) Parkallee 1, D-23845, Borstel, Germany

2. INVENTOR'S SIGNATURE: Date 20/02/01
   Inventor's Name (typed) Johannes (First) DEX (Middle Initial) Gerdes (Family Name) Germany (Country of Citizenship)
   Residence (City) Feldhorst (State) Germany
   Post Office Address (Include Zip Code) Steinfeld 79, D-21838, Feldhorst, Germany

3. INVENTOR'S SIGNATURE: A. Böhle Date 20/2/01
   Inventor's Name (typed) Andreas (First) DEX (Middle Initial) Böhle (Family Name) Germany (Country of Citizenship)
   Residence (City) Groß Grönau (State) Germany
   Post Office Address (Include Zip Code) Fasanenring 2, D-23627, Groß Gronau, Germany

4. INVENTOR'S SIGNATURE: Date
   Inventor's Name (typed) Irina (First) Middle Initial Deinert (Family Name) Germany (Country of Citizenship)
   Residence (City) Lübeck (State) Germany
   Post Office Address (Include Zip Code) Ottermoor 13, D-23560, Lübeck, Germany

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

[ ] Declaration Submitted with Initial Filing or [X] Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e) required)

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED "ANTISENSE OLIGONUCLEOTIDES FOR TREATING PROLIFERATING CELLS", the specification of which was filed on November 21, 2000 as Attorney Docket No. 661-50303, which is a U.S. National Phase application of PCT International Application No. PCT/EP99/03451.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 including for continuation-in-part applications, material information which becomes available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a) -(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international Application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)			Priority Claimed	Certified Copy Attached?	
Number	Country	Foreign Filing Date (MM/DD/YYYY)		Yes	No
PCT/EP99/03451		May 20, 1999	Yes		
198 22 954.2	DE	May 22, 1998	Yes		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the registered practitioners represented by **Customer No.: 20736** to prosecute this application and transact all business in the U.S. Patent and Trademark Office in connection therewith. Direct all correspondence to **Farkas & Manelli, PLLC** at **Customer No.: 20736**.

1. INVENTOR'S SIGNATURE: _____ Date _____
Inventor's Name (typed) Hans-Dieter (First) Middle Initial Vlad (Family Name) Germany (Country of Citizenship)
Residence (City) Borstel (State) Germany
Post Office Address (Include Zip Code) Parkallee - D-23845, Borstel, Germany

2. INVENTOR'S SIGNATURE: _____ Date _____
Inventor's Name (typed) Johannes (First) Middle Initial Geroes (Family Name) Germany (Country of Citizenship)
Residence (City) Feldhorst (State) Germany
Post Office Address (Include Zip Code) Sternfeld 29, D-23858, Feldhorst, Germany

3. INVENTOR'S SIGNATURE: _____ Date _____
Inventor's Name (typed) Andreas (First) Middle Initial Bühle (Family Name) Germany (Country of Citizenship)
Residence (City) Groß Grönau (State) Germany
Post Office Address (Include Zip Code) Eisenbeering 2, D-23627, Groß Grönau, Germany

4. INVENTOR'S SIGNATURE: [signature] Date 20.02.2001
Inventor's Name (typed) Inga (First) Middle Initial Ehrhen-Deinert (Family Name) Germany (Country of Citizenship)
Residence (City) Lübeck (State) Germany
Post Office Address (Include Zip Code) ~~Quellenstr. 32, D-23560, Lübeck, Germany~~ Postfach 43, D-22964 Siemsdorf

GESAMT SEITEN 05